UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA - DESIGNATION FORM to be used by counsel to indicate the category of the case of the purpose of assignment to the appropriate calendar.

Address of Plaintiff: 7006 Dorsam Way, Ambler, PA 19002

Address of Defendant: 3141 Chestnut Street, Philadelphia, Pennsylvania

Place of Accident, Incident or Transaction:

Does this case involve multi-district litigation possibilities?

RELATED CASE, IF ANY

Case Number: _____ Judge: _____ Date Terminated: _____

Civil Cases are deemed related when yes is answered to any of the following questions:

1. Is this case related to property included in an earlier numbered suit pending or within one year previously terminated action in this court? Yes ☐ No ■
2. Does this case involve the same issue of fact or grow out of the same transaction as a prior suit pending or within one year previously terminated action in this court? Yes ☐ No ■
3. Does this case involve the validity or infringement of a patent already in suit or any earlier numbered case pending or within one year previously terminated action in this court? Yes ☐ No ■

CIVIL: (Place √ in ONE CATEGORY ONLY)

A. *Federal Question Cases:*

1. ☐ Indemniity Contract, Marine Contract, and All Other Contracts
2. ☐ FELA
3. ☐ Jones Act-Personal Injury
4. ☐ Antitrust
5. ■ Patent
6. ☐ Labor-Management Relations
7. ☐ Civil Rights
8. ☐ Habeas Corpus
9. ☐ Securities Act(s) Cases
10. ☐ Social Security Review Cases
11. ☐ All other Federal Question Cases (Please specify)

B. *Diversity Jurisdiction Cases:*

1. ☐ Insurance Contract and Other Contracts
2. ☐ Airplane Personal Injury
3. ☐ Assault, Defamation
4. ☐ Marine Personal Injury
5. ☐ Motor Vehicle Personal Injury
6. ☐ Other Personal Injury (Please Specify)
7. ☐ Products Liability
8. ☐ Products Liability - Asbestos
9. ☐ All other Diversity Cases

Idea Misappropriation

ARBITRATION CERTIFICATION

I, **Frederick A. Tecce**, counsel of record do hereby certify:

■ Pursuant to Local Civil Rule 53.2, Section 3(c)(2), that to the best of my knowledge and belief, the damages recoverable in this civil action case exceed the sum of $150,000.00 exclusive of interest and cost.

☐ Relief other than monetary damages is sought.

Date: August 28, 2009 Frederick A. Tecce 47298

Attorney-at Law Attorney I.D. #

I certify that, to my knowledge, the within case is not related to any case now pending or within one year previously terminated action in this court except as noted above.

Date: August 28, 2009 47298

Attorney-at Law Attorney I.D. #

UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA - DESIGNATION FORM to be used by counsel to indicate the category of the case of the purpose of assignment to the appropriate calendar.

Address of Plaintiff: 7006 Dorsam Way, Ambler, PA 19002

Address of Defendant: 3141 Chestnut Street, Philadelphia, Pennsylvania

Place of Accident, Incident or Transaction:

Does this case involve multi-district litigation possibilities?

RELATED CASE, IF ANY

Case Number: _____ Judge: _____ Date Terminated: _____

Civil Cases are deemed related when yes is answered to any of the following questions:

1. Is this case related to property included in an earlier numbered suit pending or within one year previously terminated action in this court? Yes ☐ No ■
2. Does this case involve the same issue of fact or grow out of the same transaction as a prior suit pending or within one year previously terminated action in this court? Yes ☐ No ■
3. Does this case involve the validity or infringement of a patent already in suit or any earlier numbered case pending or within one year previously terminated action in this court? Yes ☐ No ■

CIVIL: (Place √ in ONE CATEGORY ONLY)

A. *Federal Question Cases:*

1. ☐ Indemniity Contract, Marine Contract, and All Other Contracts
2. ☐ FELA
3. ☐ Jones Act-Personal Injury
4. ☐ Antitrust
5. ■ Patent
6. ☐ Labor-Management Relations
7. ☐ Civil Rights
8. ☐ Habeas Corpus
9. ☐ Securities Act(s) Cases
10. ☐ Social Security Review Cases
11. ☐ All other Federal Question Cases (Please specify)

B. *Diversity Jurisdiction Cases:*

1. ☐ Insurance Contract and Other Contracts
2. ☐ Airplane Personal Injury
3. ☐ Assault, Defamation
4. ☐ Marine Personal Injury
5. ☐ Motor Vehicle Personal Injury
6. ☐ Other Personal Injury (Please Specify)
7. ☐ Products Liability
8. ☐ Products Liability - Asbestos
9. ☐ All other Diversity Cases

Idea Misappropriation

ARBITRATION CERTIFICATION

I, **Frederick A. Tecce**, counsel of record do hereby certify:

■ Pursuant to Local Civil Rule 53.2, Section 3(c)(2), that to the best of my knowledge and belief, the damages recoverable in this civil action case exceed the sum of $150,000.00 exclusive of interest and cost.

☐ Relief other than monetary damages is sought.

Date: **August 28, 2009** Frederick A. Tecce **47298**

Attorney-at Law Attorney I.D. #

I certify that, to my knowledge, the within case is not related to any case now pending or within one year previously terminated action in this court except as noted above.

Date: **August 28, 2009** **47298**

Attorney-at Law Attorney I.D. #

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

CASE MANAGEMENT TRACK DESIGNATION FORM

BIOTECHNOLOGY, LLC	:	CIVIL ACTION
	:	
v.	:	
CIBA VISION CORP., *et al.*	:	
	:	NO.

In accordance with the Civil Justice Expense and Delay Reduction Plan of this Court, counsel for plaintiff shall complete a Case management Track Designation Form in all civil cases at the time of filing the complaint and serve a copy on all defendants. (See § 1:03 of the plan set forth on the reverse side of this form.) In the event that a defendant does not agree with the plaintiff regarding said designation, that defendant shall, with its first appearance, submit to the clerk of court and serve on the plaintiff and all other parties, a case management track designation form specifying the track to which that defendant believes the case should be assigned.

SELECT ONE OF THE FOLLOWING CASE MANAGEMENT TRACKS:

(a)	Habeas Corpus – Cases brought under 28 U.S.C. §2241 through §2255.	( )
(b)	Social Security – Cases requesting review of a decision of the Secretary of Health and Human Services Denying plaintiff Social Security Benefits.	( )
(c)	Arbitration – Cases required to be designated for arbitration under Local Civil Rule 8.	( )
(d)	Asbestos – Cases involving claims for personal injury or property damage from exposure to asbestos.	( )
(e)	Special Management – Cases that do not fall into tracks (a) through (d) that are commonly referred to as complex and that need special or intense management by the court. (See reverse side of this form for a detailed explanation of special management cases.)	( )
(f)	Standard Management – Cases that do not fall into any one of the other tracks.	(X)

August 28, 2009

Attorney-at-law

Frederick A. Tecce
Attorney for Plaintiff

(Civ. 660)
1/92

(a) The clerk of court will assign cases to tracks (a) through (d) based on the initial pleading.

(b) In all cases not appropriate for assignment by the clerk of court to tracks (a) through (d), the plaintiff shall submit to the clerk of court and serve with the complaint on all defendants a case management track designation form specifying that the plaintiff believes the case requires Standard Management or Special Management. In the event that a defendant does not agree with the plaintiff regarding said designation, that defendant shall, with its first appearance, submit to the clerk of court and serve on the plaintiff and all other parties, a case management track designation form specifying the track to which that defendant believes the case should be assigned.

(c) The court may, on its own initiative or upon the request of any party, change the track assignment of any case at any time.

(d) Nothing in this Plan is intended to abrogate or limit a judicial officer's authority in any case pending before that judicial officer, to direct pretrial and trial proceedings that are more stringent than those of the Plan and that are designed to accomplish cost and delay reduction.

(e) Nothing in this Plan is intended to supersede Local Civil Rules 3 or 7, or the procedure for random assignment of Habeas Corpus and Social Security cases referred to magistrate judges of the court.

SPECIAL MANAGEMENT CASE ASSIGNMENTS
(See § 1.02(e) Management Track Definitions of the Civil Justice Expense and Delay Reduction Plan)

Special management cases will usually include that class of cases commonly referred to as "complex litigation" as that term has been used in the Manuals for Complex Litigation. The first manual was prepared in 1969 and the Manual for Complex Litigation Second, MCL 2d was prepared in 1985. This term is intended to include cases that present unusual problems and require extraordinary treatment. See §0.1 of the first manual. Cases may require special or intense management by the court due to one or more of the following factors: (1) large number of parties; (2) large number of claims or defenses; (3) complex factual issues; (4) large volume of evidence; (5) problems locating or preserving evidence; (6) extensive discovery; (7) exceptionally long time needed to prepare for disposition; (8) decision needed within an exceptionally short time; and (9) need to decide preliminary issues before final disposition. It may include two or more related cases. Complex litigation typically includes such cases as antitrust cases; cases involving a large number of parties or an unincorporated association of large membership; cases involving requests for injunctive relief affecting the operation of large business entities; patent cases; copyright and trademark cases; common disaster cases such as those arising from aircraft crashes or marine disasters; actions brought by individual stockholders; stockholder's derivative and stockholder's representative actions; class actions or potential class actions; and other civil (and criminal) cases involving unusual multiplicity or complexity of factual issues. See §0.22 of the first Manual for Complex Litigation and Manual for Complex Litigation Second, Chapter 33.

JS 44 (Rev. 3/99) **CIVIL COVER SHEET**

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

PLAINTIFF(S)
BIOTECHNOLOGY, LLC

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES

(c) Attorney's (Firm Name, Address, and Telephone Number)
Frederick A. Tecce, Esquire, McShea Tecce, PC
1717 Arch Street, 28th Floor, Bell Atlantic Tower
Philadelphia, PA 19103 (215) 599-0800

DEFENDANT(S)
CIBS VISION CORP. and DREXEL UNIVERSITY

(c) County of Residence of First Listed _____
((IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE L A N D I N V O LVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in O ne Box Only)

- ☐ 1 U.S. Government Plaintiff
- ■ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

(Place an "X " in One Box for Plaintiff and One Box for Defendant) (For Diversity Cases Only)

	PLT	DEF		PLT	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *or* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACTS
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contracts
- ☐ 195 Contract Product Liability

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 U.S.C.
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

BANKRUPTCY
- ☐ 422 Appeal 28 U.S.C. 158
- ☐ 423 Withdrawal 28 U.S.C. 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ■ 830 Patent
- ☐ 840 Trademark

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 U.S.C. 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Conditions

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 795 Empl. Ret. Inc. Security Act

SOCIAL SECURITY
- ☐ 861 HIA (13 95ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIW C/DIW W (405(g))
- ☐ 865 RSI (405)(g))

FEDERAL TAXSUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

V. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

■ 1 Original Proceeding	☐ 2 Removed from State Court	☐ 3 Remanded from Appellate Court	☐ 4 Reinstated or Reopened	☐ 5 Transferred from Another District Specify)	☐ 6 Multi district Litigation	☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION (Cite the U.S. Civil State under which you are filing and write brief statement of cause. Do not cite jurisdictional statutes unless diversity)
35 U.S.C. § 101, *et seq.*

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 DEMAND $ Excess of $ CHECK YES only if demanded in complaint JURY DEMAND: ■ Yes ☐ No

VIII. RELATED CASE(S) (See Instructions) IF ANY N/A

Date August 28, 2009

Signature of Attorney of Record

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

BIOTECHNOLOGY, LLC 7006 Dorsam Way Ambler, Pennsylvania 19002 ***Plaintiff,***	:	
v.	:	
CIBA VISION CORPORATION 11460 Johns Creek Parkway Duluth, Georgia 30097 ***Defendant***	:	**CIVIL ACTION** **NO: 09-CV-_____**
and	:	
DREXEL UNIVERSITY 3141 Chestnut Street Philadelphia, Pennsylvania 19104 ***Defendant*** ***and Involuntary Plaintiff.***	:	**JURY TRIAL DEMANDED**

COMPLAINT

COMES NOW, Plaintiff BioTechnology, LLC ("BioTechnology"), by and through its undersigned counsel for its complaint against Defendant CIBA Vision Corporation ("CIBA") and Defendant/ Involuntary Plaintiff Drexel University ("Drexel"), and alleges as follows:

THE PARTIES

1. This is an action for patent infringement pursuant to 35 U.S.C. §§ 101, *et seq.*

2. Plaintiff BioTechnology is a Delaware limited liability corporation with an address of 7006 Dorsam Way, Ambler, Pennsylvania 19002.

3. Upon information and belief, Defendant CIBA is a Delaware corporation having a principal place of business at 11460 Johns Creek Parkway, Duluth, Georgia 30097.

4. Upon information and belief, Defendant/Involuntary Plaintiff Drexel is a private university having a principal address of 3141 Chestnut Street, Philadelphia, Pennsylvania.

Drexel is a joint owner of the patents-in-suit in this action. Pursuant to FEDERAL RULE OF CIVIL PROCEDURE 19(a), Drexel has been named as a defendant and involuntary plaintiff because it has refused to join as a party plaintiff with BioTechnology, and because BioTechnology has separate claims against Drexel resulting from its refusal, all of which are set forth below.

JURISDICTION AND VENUE

5. This action arises under the Patent Laws of the United States, Title 35, United States Code § 101, *et seq*. The Court's jurisdiction over this action is proper under 35 U.S.C. § 271 *et seq*., and 28 U.S.C. §§ 1331, 1338(a), and 1367(a).

6. Personal jurisdiction exists generally over CIBA because it has sufficient minimum contacts with the forum as a result of business conducted within the Commonwealth of Pennsylvania and this judicial district. Personal jurisdiction also exists specifically over CIBA because of its conduct in making, using, selling, offering for sale, and importing products that practice or are manufactured by processes that practice the patents asserted herein, directly, contributorily, and by inducement, within the United States, the Commonwealth of Pennsylvania and this judicial district.

7. Upon information and belief, the accused products are also offered for sale through the CIBA website at www.us.cibavision.com in the Commonwealth of Pennsylvania and the Eastern District of Pennsylvania.

8. Personal jurisdiction exists generally over Drexel because it resides within the district.

9. Venue is proper in this Court under 28 U.S.C. §§ 1391(b), (c), and (d), and 28 U.S.C. § 1400(b).

FACTUAL BACKGROUND

10. BioTechnology is a scientific research company located in Ambler, Pennsylvania.

11. Ophthalmic Research Corporation ("ORC") was a scientific research company located in Philadelphia, Pennsylvania that operated during the early-1980s to mid-2000s.

12. On or about March 5, 1984, ORC and Drexel executed the Joint Research Program Agreement ("Research Agreement"), which stated "all Inventions . . . shall be jointly owned by Drexel and ORC, and each party shall have an equal, undivided, one-half interest . . . as well as in and to patent applications and patents thereon . . . ." The Research Agreement defined "Inventions" as "any invention, discovery or improvement, whether or not patentable, conceived solely or jointly by Drexel personnel . . . or jointly by Drexel personnel with one or more personnel . . . of ORC . . . ." A true and correct copy of the Research Agreement is attached hereto as Exhibit A.

13. The Research Agreement resulted in issuance of U.S. Patent No. 5,080,924 ("the '924 Patent"); U.S. Patent No. 5,260,093 ("the '093 Patent"); U.S. Patent No. 5,326,584 ("the '584 Patent"); and U.S. Patent No. 5,578,079 ("the '079 Patent") (collectively the "Research Patents").

14. Under Paragraph 7 of the Research Agreement, Drexel agreed "to cooperate fully with ORC in the prosecution of patent applications on any such Inventions and in ***any litigation*** involving any patent issued thereon," and "to do everything considered by ORC to be appropriate, desirable and necessary to assure to ORC the rights granted" under the Research Agreement.

15. On or about March 16, 2004, ORC merged into Bio-Cellular, LLC ("Bio-Cellular"), a New Jersey limited liability company, and subsequently assigned all rights, title,

and interest in the Research Patents, including the right to sue and recover for past infringement, to BioTechnology.

16. On or about December 17, 2008, Bio-Cellular executed a *nunc pro tunc* assignment of all rights, title and interest in the Research Patents, including the right to sue, and recover for past infringement to BioTechnology.

17. On or about June 10, 2009, Bio-Cellular merged into BioTechnology.

18. On or about August 11, 2009, Bio-Cellular, as successor-in-interest to ORC, assigned to BioTechnology all rights, title and interest in the Research Agreement and confirmed that any interests in the Research Patents were assigned to and in favor of BioTechnology.

19. Attorneys for BioTechnology conferenced with attorneys from Drexel on several occasions from about May 19, 2009 to about July 6, 2009 in an attempt to convince Drexel to honor its contractual obligations under the Research Agreement. The discussions were not successful. Drexel did not agree to unequivocally "cooperate fully ... in any litigation involving any patent," as required by the Research Agreement.

20. Despite its specific agreement that it would do so, Drexel still refuses to join as a party plaintiff in this or any action enforcing the Research Patents. As a result, Drexel is named as a defendant and involuntary plaintiff pursuant to FEDERAL RULE OF CIVIL PROCEDURE 19(a).

COUNT I
INFRINGEMENT OF THE CLAIMS OF U.S. PATENT NO. 5,080,924

21. BioTechnology and Drexel are the owners of all rights, title, and interest in and under the '924 Patent, titled "Method of Making Biocompatible, Surface Modified Materials," which was duly and legally issued on January 14, 1992. A true and correct copy of the '924 Patent is attached hereto as Exhibit B.

22. The '924 Patent was valid and enforceable during its term.

23. Upon information and belief, CIBA had been infringing by practicing the methods of the claims of the '924 Patent, without authority, by making, using, importing, selling, or offering to sell in or into the United States, without authority, products that are covered by or are manufactured by processes that are covered by, the claims of the '924 Patent, including infringement under 35 U.S.C. § 271(g).

24. By practicing the methods of the claims of the '924 Patent, without authority, and/or by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '924 Patent, CIBA had been inducing infringement of the claims of the '924 Patent by others, pursuant to 35 U.S.C. § 271(b).

25. By practicing the methods of the claims of the '924 Patent, without authority, or by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '924 Patent that are not staple articles of commerce having a substantial non-infringement use, CIBA had been contributing to the infringement of the claims of the '924 Patent by others, pursuant to 35 U.S.C. § 271(c).

26. As a direct and proximate result of CIBA's acts of patent infringement, Plaintiff had been injured and sustained substantial damages in an amount not presently known but in no event less than a reasonable royalty.

27. Upon information and belief, CIBA's infringement was willful so as to warrant enhancement of damages awarded as a result of its infringement.

28. All applicable marking requirements of 35 U.S.C. § 287 with respect to the '924 Patent had been complied with.

COUNT II
INFRINGEMENT OF THE CLAIMS OF U.S. PATENT NO. 5,260,093

29. BioTechnology and Drexel are the owners of all rights, title, and interest in and under the '093 Patent, titled "Method of Making Biocompatible, Surface Modified Materials," which was duly and legally issued on November 9, 1993. A true and correct copy of the '093 Patent is attached hereto as Exhibit C.

30. The '093 Patent was valid and enforceable during its term.

31. Upon information and belief, CIBA had been infringing by practicing the methods of the claims of the '093 Patent, without authority, by making, using, importing, selling, or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the methods of the claims of the '093 Patent, including infringement under 35 U.S.C. § 271(g).

32. By practicing the methods of the claims of the '093 Patent, without authority, or by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '093 Patent, CIBA had been inducing infringement of the claims of the '093 Patent by others, pursuant to 35 U.S.C. § 271(b).

33. By practicing the methods of the claims of the '093 Patent, without authority, or by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '093 Patent that are not staple articles of commerce having a substantial non-infringement use, CIBA had been contributing to the infringement of the claims of the '093 Patent by others, pursuant to 35 U.S.C. § 271(c).

34. As a direct and proximate result of CIBA's acts of patent infringement, Plaintiff had been injured and sustained substantial damages in an amount not presently known but in no event less than a reasonable royalty.

35. Upon information and belief, CIBA's infringement was willful so as to warrant enhancement of damages awarded as a result of its infringement.

36. All applicable marking requirements of 35 U.S.C. § 287 with respect to the '093 Patent had been complied with.

COUNT III
INFRINGEMENT OF THE CLAIMS OF U.S. PATENT NO. 5,326,584

37. Plaintiff BioTechnology and Drexel are the owners of all rights, title, and interest in and under the '584 Patent titled "Biocompatible, Surface Modified Materials and Method of Making The Same," which was duly and legally issued on July 5, 1994. A true and correct copy of the '584 Patent is attached hereto as Exhibit D.

38. The '584 Patent was valid and enforceable during its term.

39. Upon information and belief, CIBA had been infringing by practicing the methods of the claims of the '584 Patent, without authority, by making, using, importing, selling, or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '584 Patent, including infringement under 35 U.S.C. § 271(g).

40. By practicing the methods of the claims of the '584 Patent, without authority, or by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '584 Patent, CIBA had been inducing infringement of the claims of the '584 Patent by others, pursuant to 35 U.S.C. § 271(b).

41. By practicing the methods of the claims of the '584 Patent, without authority, or by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '584 Patent that are not staple articles of commerce having a substantial non-infringement use, CIBA had been contributing to the infringement of the claims of the '584 Patent by others, pursuant to 35 U.S.C. § 271(c).

42. As a direct and proximate result of CIBA's acts of patent infringement, Plaintiff had been injured and sustained substantial damages in an amount not presently known but in no event less than a reasonable royalty.

43. Upon information and belief, CIBA's infringement was willful so as to warrant enhancement of damages awarded as a result of its infringement.

44. All applicable marking requirements of 35 U.S.C. § 287 with respect to the '584 Patent has been complied with.

COUNT IV
INFRINGEMENT OF THE CLAIMS OF U.S. PATENT NO. 5,578,079

45. BioTechnology and Drexel are the owners of all rights, title, and interest in and under the '079 Patent, titled "Biocompatible, Surface Modified Materials," which was duly and legally issued on November 26, 1996. A true and correct copy of the '079 Patent is attached hereto as Exhibit E.

46. The '079 Patent is valid and enforceable.

47. Upon information and belief, CIBA has been infringing by practicing the methods of the claims of the '079 Patent, without authority, by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are

manufactured by processes that practice the claims of the '079 Patent, including infringement under 35 U.S.C. § 271(g).

48. By practicing the methods of the claims of the '079 Patent, without authority, or by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '079 Patent, CIBA has been inducing infringement of the claims of the '079 Patent by others, pursuant to 35 U.S.C. § 271(b).

49. By practicing the methods of the claims of the '079 Patent, without authority, and/or by making, using, importing, selling, and/or offering to sell in or into the United States, without authority, products that practice or are manufactured by processes that practice the claims of the '079 Patent that are not staple articles of commerce having a substantial non-infringement use, CIBA has been contributing to the infringement of the claims of the '079 Patent by others, pursuant to 35 U.S.C. § 271(c).

50. As a direct and proximate result of CIBA's acts of patent infringement, Plaintiff has been injured and has sustained substantial damages in an amount not presently known but no event less than a reasonable royalty.

51. Upon information and belief, CIBA's infringement has been willful so as to warrant enhancement of damages awarded as a result of its infringement.

52. All applicable marking requirements of 35 U.S.C. § 287 with respect to the '079 Patent had been complied with.

COUNT V
BREACH OF CONTRACT
(BIOTECHNOLOGY V. DREXEL)

53. The Research Agreement constitutes a contract between Drexel and

BioTechnology, who is the successor-in-interest of ORC's rights under the Research Agreement.

54. Drexel has breached and continues to breach the Research Agreement by its continued refusal to cooperate with BioTechnology to prosecute and enforce the Research Patents.

55. The foregoing breach of contract constitutes material breaches that have caused substantial damage to BioTechnology. BioTechnology is entitled to a judgment against Drexel for damages caused by Drexel's refusal and continued breach of contract to cooperate with BioTechnology, including lost revenues from potential infringers by Drexel's delay in enforcing the Research Patents.

56. All conditions precedent by BioTechnology have been satisfied.

COUNT VI
SPECIFIC PERFORMANCE OF CONTRACT
(BIOTECHNOLOGY V. DREXEL)

57. As a result of Drexel's continued refusal to cooperate with BioTechnology as joint owners to enforce the Research Patents, BioTechnology does not have an adequate remedy at law. Accordingly, interest and justice dictate that specific performance of contract be granted. Specifically, BioTechnology prays that Drexel be compelled to cooperate fully pursuant to the terms and conditions agreed upon in the Research Agreement and voluntarily assist BioTechnology to enforce the Research Patents.

COUNT VII
RESCISSION ON CONTRACT
(BIOTECHNOLOGY V. DREXEL)

58. As a result of Drexel's continued refusal to cooperate with BioTechnology as joint owners to enforce the Research Patents, BioTechnology does not have an adequate remedy at law and such breaches by Drexel constitute material breaches of the Research Agreement.

Accordingly, interest and justice dictate that rescission of contract be granted. Specifically, Biotechnology prays that it be excused from any further obligations under the Research Agreement and that the Research Agreement be rescinded.

COUNT VIII
INJUNCTIVE RELIEF
(BIOTECHNOLOGY V. DREXEL)

59. BioTechnology will suffer irreparable injury if Drexel is not preliminarily and permanently enjoined because BioTechnology will continue to be deprived of licensing revenue should Drexel enforce the Research Patents without conferring with BioTechnology. Moreover, because the Research Agreement specifically states that both BioTechnology and Drexel are joint owners of the Research Patents, BioTechnology will be deprived of the opportunity to license this technology to other potential licensees should Drexel license these patents independently. At present, these damages are largely incalculable, and therefore BioTechnology has no adequate remedy at law.

60. The Research Foundation therefore requests that the Court enter preliminary and permanent injunctions:

(1) Enjoining Drexel and its agents, servants, employees, and representatives, and all others acting in combination with them from licensing and/or enforcing the Research Patents, except in this action; and

(2) Requiring Drexel, and its agents, servants, employees, and representatives, and all others acting in combination with them to return to BioTechnology all documentation (including paper files and electronic storage media) containing, evidencing, using, or incorporating the Research Patents.

WHEREFORE, Plaintiff Biotechnology, LLC respectfully requests that judgment be entered in its favor and against Defendant CIBA Vision Corporation and Defendant/Involuntary Plaintiff Drexel University and and that the Court grants the following relief to the Plaintiff:

A. Declare that CIBA has infringed the claims of the '924 Patent, the '093 Patent, the '584 Patent, and the '079 Patent;

B. Judgment for BioTechnology's actual damages caused by CIBA's patent infringement but in no event less than a reasonable royalty;

C. Injunctive relief, both preliminary and permanent, enjoining CIBA from direct infringement, inducement of infringement, and contributory infringements of the claims of the '924 Patent, the '093 Patent, the '584 Patent, and the '079 Patent.

D. Judgment that CIBA has willfully infringed the '924 Patent, the '093 Patent, the '584 Patent, and the '079 Patent and award BioTechnology treble damages as provided in 35 U.S.C. § 284;

E. Judgment that this is an exceptional case and award BioTechnology its expenses, costs, and attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285, including pre-judgment and post-judgment interest on any damages.

F. Judgment that Drexel breached the Research Agreement;

G. Judgment that Drexel's breach constituted a material breach of the Research Agreement;

H. Judgment that the Research Agreement be rescinded and that BioTechnology be excused from any further obligations under the Research Agreement;

I. Order that Drexel specifically perform its obligations to cooperate with BioTechnology in enforcement of the Research Patents;

J. Injunctive relief, both preliminary and permanent:

(a) Enjoining Drexel and its agents, servants, employees, and representatives, and all others acting in combination with them from licensing the Research Patents, except in this action; and

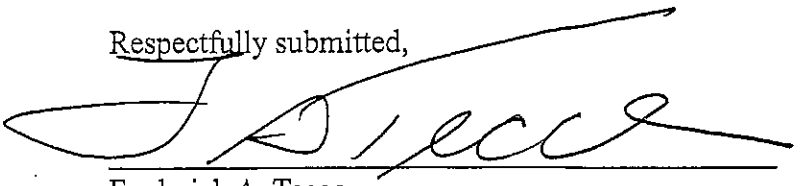
(b) Requiring Drexel and its agents, servants, employees, and representatives, and all others acting in combination with them to return to BioTechnology all documentation (including paper files and electronic storage media) containing, evidencing, using, or incorporating the Research Patents.

K. Judgment for BioTechnology's actual damages caused by Drexel's breach of contract;

L. Judgment and award any such other and further relief as the Court deems just and proper.

Dated: August 28, 2009

Respectfully submitted,



Frederick A. Tecce
McShea\Tecce, P.C.
The Bell Atlantic Tower - 28th Floor
1717 Arch Street
Philadelphia, PA 19103
215.599.0800 Telephone
215.599.0888 Facsimile

Attorneys for Plaintiff
BioTechnology, LLC

Of Counsel:
Michael W. Shore
Texas Bar No. 18294915
Alfonso Garcia Chan
Texas Bar No. 24012408
Rajkumar Vinnakota
Texas Bar No. 24042337
Patrick Traister
Texas Bar No. 24046991
SHORE CHAN BRAGALONE LLP
901 Main Street, Suite 3300
Dallas, Texas 75202
214.593.9110 Telephone
214.593.9111 Facsimile

EXHIBIT A

JOINT RESEARCH PROGRAM AGREEMENT
between
DREXEL UNIVERSITY
and
OPHTHALMIC RESEARCH CORPORATION

THIS AGREEMENT sets forth the relationship between Ophthalmic Research Corporation, 5001 Frankford Avenue, Philadelphia, Pennsylvania 19124 (hereinafter referred to as "ORC") and Drexel University, 32nd and Chestnut Streets, Philadelphia, Pennsylvania 19104 (hereinafter referred to as "Drexel"), whereby ORC and Drexel agree to enter into a Joint Research Program for the purpose of conducting cooperative research in medical and related fields, particularly ophthalmology (hereinafter referred to as "Program"), subject to the following terms and conditions:

1. Scope of Work. Drexel agrees to provide personnel, facilities and equipment as required to conduct the Program. Drexel agrees to use its best efforts, skill, knowledge and experience to advance the objectives of the Program. Any services Drexel plans on performing for other parties during the term of this Agreement which might directly or indirectly conflict with the interests of ORC shall be discussed with ORC and the parties shall agree upon measures to avoid conflict, including where possible assignment of different personnel to projects which directly or indirectly conflict with the interests of ORC.

2. Period of Performance. The Program shall commence on or about January 1, 1984 and shall be renewed annually if notice of termination has not been tendered in writing by either party.

3. Payments by ORC. ORC agrees to pay to Drexel the funds required for each individual research project pursued under the Program (hereinafter "Research Project"). Payment will be made to Drexel in accordance with the payment schedule stated in each specific Research Project Agreement which will more fully define the Research Project(s). Any funds paid to Drexel under each specific Research Project Agreement which are not used by Drexel in the course of the Research Project shall be returned to ORC.

4. Confidential Information Exchange. ORC will provide certain information and technology to Drexel which relate

to the objectives of each Research Project and which may previously have been conceived and/or developed by ORC (hereinafter collectively referred to as "Confidential Information"). Drexel agrees not to disclose any of this Confidential Information to any persons not owing an obligation of secrecy to either Drexel or ORC without written consent of ORC, which consent shall not be unreasonably withheld. The Confidential Information shall not include information which:

(a) At the time it is so made available is a matter of common knowledge and in the public domain; or

(b) After it is so made available becomes a matter of common knowledge and in the public domain other than through the actions of Drexel; or

(c) Was already known to Drexel, as shown by written records, at the time made available; or

(d) Was independently received by Drexel from a third party, as evidenced by written records, having no legal duty to ORC to hold such information in confidence.

5. Publication Rights. Drexel shall have the right to publish the results of any Research Project provided Drexel shall first have complied with the duty to (i) notify ORC of its intent to publish, (ii) furnish ORC with an advance copy of each manuscript at least sixty (60) days before it is submitted for publication, (iii) assure ORC that the publication does not contain any ORC Confidential Information, and (iv) delay publication upon request of ORC for at least six (6) months following ORC's receipt of such notification. It is understood that any and all of the foregoing provisions may be waived by ORC in writing and that ORC will not unreasonably withhold its consent.

6. Disclosures. "Invention" shall mean any invention, discovery or improvement, whether or not patentable, conceived solely or jointly by Drexel personnel (faculty, students and/or staff) or jointly by Drexel personnel with one or more personnel (employees, officers and/or consultants) of ORC during the term of this Agreement and in the performance of services hereunder. Drexel agrees to promptly notify ORC in writing of all Inventions developed hereunder.

7. Patent Rights. All Inventions, as defined above, made or conceived during the term of this Agreement, which relate to the subject of this Agreement and which result from or arise out of the services performed by Drexel pursuant to a

specific Research Project Agreement, shall be jointly owned by Drexel and ORC, and each party shall have an equal, undivided, one-half interest in and to such Invention, as well as in and to patent applications and patents thereon in all countries, unless expressly waived by either party. As a matter of convenience, ORC will file any and all patent applications on such Inventions, prosecute said patent applications and obtain the patents in the name of both parties. Any and all documents necessary or desirable to carry out the provisions of this paragraph shall be executed by Drexel and its personnel without charge, and Drexel agrees to cooperate fully with ORC in the prosecution of patent applications on any such Inventions and in any litigation involving any patent issued thereon. To this end, Drexel and its personnel agree to do everything considered by ORC to be appropriate, desirable and necessary to assure to ORC the rights granted hereunder.

ORC shall have the right of first refusal to obtain an exclusive license with the right to grant sublicenses to Drexel's interest in and to any Invention (including any patent applications and any patents that may issue thereon), whether or not any personnel of ORC is a co-inventor. In consideration for the exclusive license granted to ORC by Drexel relating to any such Invention, ORC agrees to pay to Drexel a royalty, negotiated in good faith, of not less than one-fifth (1/5) and not more than one-third (1/3), of the net royalty income earned by ORC on any such Invention. Net income for the purposes of this Agreement shall mean all royalty income less reasonable expenses borne by ORC in preparing, prosecuting and maintaining patent applications and patents on said Invention. If ORC elects not to obtain an exclusive license, Drexel shall grant ORC a fully paid-up non-exclusive license of Drexel's interest in and to such Inventions and any patents which may issue thereon and in which ORC is not exclusively licensed.

Nothing contained in this Paragraph 7 shall be deemed to grant either directly or by implication, estoppel, or otherwise, any license under any patents or patent application arising out of any other invention of either party.

8. Confidential Information Developed. It is envisioned that Drexel will develop confidential information as a result of its research efforts under each Research Project Agreement. Such Drexel-developed confidential information shall be promptly disclosed to ORC and shall become the property of ORC and shall be considered ORC Confidential Information for the purpose of this Agreement and subject to the provisions of Paragraph 4 hereof.

9. Indemnification. ORC agrees to indemnify, defend and save harmless Drexel and Drexel personnel against any liability, including costs and expenses, for violation of proprietary rights, or right of privacy, arising out of ORC's publication, translation, reproduction, delivery, performance, use or disposition of any data or research results furnished under this Agreement.

10. Termination. Upon the occurrence of a breach, either party shall have the right to terminate this Agreement by giving notice in writing to the other party that this Agreement will be terminated and cancelled in thirty (30) days and specifying the nature of the breach. During the thirty (30) day period after the date of such notice, the party receiving such notice shall have the privilege of maintaining this Agreement by making good within the said thirty (30) days the breach on account of which notice was given.

11. Similar Agreements. This Agreement shall not prevent the parties from entering into similar Agreements with others except as they are bound by the terms of this Agreement and specific Research Project Agreements pursuant to this Agreement.

12. General Provisions. The rights and obligations of Paragraphs 4, 8 and 9 shall survive and continue for a period of three (3) years after any expiration or termination of this Agreement and shall bind the parties and their legal representatives, successors, heirs and assigns. The rights and obligations of Paragraph 7 shall survive and continue for the life of the respective Patent Rights. Both parties agree to comply with all applicable Federal, State and local laws, regulations and ordinances, including but not limited to the Regulations of the United States Department of Commerce relating to the Export of Technical Data and agree to obtain the required government documents and approvals prior to any export of technical data disclosed by either party or the direct product related thereto.

13. Drexel's Freedom to Provide Services. Drexel represents and warrants that it is under no obligation or restriction, nor will Drexel assume such obligation or restriction, which would in any way interfere or be inconsistent with the services to be furnished by Drexel under this Agreement.

14. Drexel's Agreement with Its Personnel. Drexel will have an appropriate agreement with each of its personnel or others whose services Drexel may require sufficient to enable Drexel to comply with all terms of this Agreement.

15. Sole Agreement. This Agreement shall supersede all prior agreements and understandings between the parties respecting the subject matter hereof. This Agreement may not be changed or terminated orally by or on behalf of either party.

OPHTHALMIC RESEARCH CORPORATION

Date: February 16, 1984

By: David B. Soll, M.D.
Title: President

DREXEL UNIVERSITY

Date: 3/5/84

By: Alvin N. Ward
Title: Vice President & Treasurer

EXHIBIT B

US005080924A

United States Patent [19]

Kamel et al.

[11] Patent Number: 5,080,924

[45] Date of Patent: Jan. 14, 1992

[54] METHOD OF MAKING BIOCOMPATIBLE, SURFACE MODIFIED MATERIALS

[75] Inventors: Ihab Kamel, Drexel Hill; David B. Soll, Rydal, both of Pa.

[73] Assignees: Drexel University; Ophthalmic Research Corporation, both of Philadelphia, Pa.

[21] Appl. No.: 342,270

[22] Filed: Apr. 24, 1989

[51] Int. Cl.[5] A61F 2/14

[52] U.S. Cl. 427/2; 427/40; 427/41; 427/45.1; 427/164; 427/333; 427/412.3; 427/412.4; 427/412.5; 523/105; 623/6

[58] Field of Search 427/2, 40, 41, 162, 427/164, 412.3, 302, 45.1, 333, 412.4, 412.5; 523/105, 106, 112, 113; 623/6, 166; 204/165

[56] References Cited

U.S. PATENT DOCUMENTS

2,999,056	9/1961	Tanner	522/118
3,228,741	1/1966	Becker	351/160 R
3,880,818	4/1975	Shen et al.	526/322
3,925,178	12/1975	Gesser et al.	204/165
3,944,709	3/1976	Levy	428/409
3,959,105	5/1976	Feneberg et al.	204/165
3,961,379	6/1976	Highgate	522/116
3,985,697	10/1976	Urbach	523/106
4,055,378	10/1977	Feneberg et al.	351/160 R
4,072,769	2/1978	Lidel	427/38
4,096,315	6/1978	Kubacki	428/412
4,122,942	10/1978	Wolfson	206/5.1
4,123,308	10/1978	Nowlin et al.	427/41
4,131,691	12/1978	Morley et al.	427/41
4,137,365	1/1979	Wydeven et al.	428/412
4,143,949	3/1979	Chen	427/41
4,189,364	2/1980	Aelion et al.	522/4
4,214,014	7/1980	Höfer et al.	427/40
4,240,163	12/1980	Galin	623/6
4,277,595	7/1981	Deichert et al.	528/26
4,312,575	1/1982	Peyman et al.	351/160 H
4,328,257	5/1982	Muehlberger et al.	427/34
4,344,981	8/1982	Imada et al.	427/40
4,405,773	9/1983	Loshaek et al.	526/318.42
4,409,258	10/1983	Feurer et al.	427/38
4,430,458	2/1984	Tighe et al.	523/108
4,463,148	7/1984	Höfer et al.	526/264
4,478,873	10/1984	Masso et al.	427/40
4,656,083	4/1987	Hoffman et al.	427/41
4,720,512	1/1988	Hu et al.	523/112
4,731,080	3/1988	Galin	623/6
4,865,870	9/1989	Hu et al.	427/2
4,885,077	12/1989	Karakelle et al.	427/41
4,919,659	4/1990	Horbett et al.	427/2
4,927,676	5/1990	Williams et al.	427/2

OTHER PUBLICATIONS

H. Yasuda, "Plasma for Modification of Polymers," *J. Macromol. Sci.-Chem., A10(3), pp. 383–420 (1976).*

Knight et al., "Surface Modification of Intraocular Lenses to Reduce Corneal Endothelial Damage," *AM Intra-Ocular Implant Soc. J*-vol. V, pp. 123–130, Apr. 1979.

Gazard et al., "Lithographic Technique Using Radiation-Induced Grafting of Acrylic Acid into Poly(-Methyl Methacrylate) Films," *Polymer Engineering and Science*, vol. 20, No. 16, pp. 1069–1072 (1980).

K. L. Mittal, "Interfacial Chemistry and Adhesion: Recent Developments and Prospects," *Pure & Appl. Chem.*, vol. 52, pp. 1295–1305 (1980).

Akovali et al., "Polymerization of Hexamethyldisiloxane by Plasma on Activated Charcoal: Investigation of Parameters," *Journal of Applied Polymer Science*, vol. 29, pp. 2617–2625 (1984).

Liu et al., "Polymethyl Methacrylate Resist Sensitivity Enhancement in X-Ray Lithography by In Situ Polymerization," *Appl. Phys. Lett.*, 44(10), pp. 973–975, May 15, 1984.

Keates et al., "Coated Intraocular Lenses," *Ophthalmic Surgery*, vol. 18, No. 9, pp. 693–697 (1987).

Primary Examiner—Shrive Beck
Assistant Examiner—Terry J. Owens
Attorney, Agent, or Firm—Panitch Schwarze Jacobs & Nadel

[57] ABSTRACT

A method of permanently modifying the surface of a substrate material so as to develop a microscopically smooth, biocompatible surface thereon comprises covalently grafting at least a first biocompatible material, preferably having pendant terminal carboxylic acid or amine groups, to the surface of the substrate material by radio frequency plasma-induced grafting. In addition, a method of permanently modifying the surface of the substrate material comprises cross-linking a second biocompatible material to the first biocompatible material grafted to the substrate material using a cross-linking agent. Further, a prosthesis used in mammals, including an intraocular lens, comprises a polymer core and at least a first biocompatible material, preferably having pendant terminal carboxylic acid or amine groups, covalently grafted to the polymer core by radio frequency plasma induction. The prosthesis used in mammals may further comprise a second biocompatible material cross-linked to the grafted first biocompatible material by a cross-linking agent.

23 Claims, No Drawings

METHOD OF MAKING BIOCOMPATIBLE, SURFACE MODIFIED MATERIALS

FIELD OF THE INVENTION

The present invention relates to methods of permanently modifying the surface of materials by plasma-induced and, where desired, post-plasma reactions to produce biocompatible, surface modified materials. In addition, the present invention relates to biocompatible, surface modified prostheses and, in particular, to a biocompatible, surface modified intraocular lens used in mammals.

BACKGROUND OF THE INVENTION

Prosthetic devices or prostheses are commonly used in medical procedures replacing or augmenting defective organs in mammals and humans, in particular, and are numerous and diverse in structure and application. Examples of prostheses include artificial joints, valve replacements, skin grafts, vascular grafts, shunts, plates and contact and intraocular lenses. Typically, prosthetic devices comprise natural and/or synthetic materials which are abrasive on the cellular level Various prostheses in current use or in experimental use comprise metals, ceramics, silicone rubbers, polyesters, polyurethanes and/or polysulfones. Synthetic polymers, such as polymethylmethacrylate (PMMA) and hydroxyethylmethacrylate (HEMA), for example, are preferred polymers for prosthetic use in general and contact lenses and intraocular lenses in particular.

PMMA, for example, has several beneficial characteristics for such prosthetic use, including excellent light transmission, good optical clarity, resistance to fluid diffusion and in vivo deterioration, ease in processing (injection molding or machining, for example) and ease in implantation, such as an intraocular lens, an artificial joint and other implantable prostheses. However, PMMA has several disadvantages in prosthetic use, including hydrophobic properties, a tendency to attach to endothelia, general cellular adhesion and a tendency to become encapsulated with fibrous tissues.

Hydrophobic and/or abrasive prostheses, especially those which are implanted, can cause tissue irritation, edema and scarring. For example, posterior lens capsule opacification is a prevalent problem among those patients who have received intraocular lens implants comprising PMMA and other hydrophobic materials.

It is desirable to modify the surface properties of such hydrophobic and/or abrasive materials without changing the beneficial characteristics thereof, by developing or enhancing surface hydrophilicity, thereby reducing abrasiveness, discouraging tissue adhesion and inhibiting cellular growth, and by developing a smooth surface. Moreover, such surface modification should be resistant to deterioration over time and should have no adverse effects on tissues and cells with which the surface modified material comes in contact.

Those skilled in the art have long recognized the need for biocompatible, surface modified materials for use in prosthetic devices and other materials. For example, U.S. Pat. No. 3,961,379 discloses a bioimplantable device manufactured from a cross-linked, swollen, hydrophilic polymer. These modified polymers must be solid and must be swellable by fluid swelling substances. Once swollen, the solid polymer is polymerized with a modifying substance by, for example, high energy particle radiation.

U.S. Pat. No. 4,189,364 discloses hydrophilic polymers formed in situ by irradiating a mixture of hydroxyalkyl methacrylate and a cross-linking agent. This patent discloses a process for forming hydrophilic polymer articles or hydrophilic polymer coatings on other substrates, such as glass or plastic, by polymerizing a hydrophilic monomer system by high energy particulate irradiation, such as accelerated electrons or nuclear particles including neutrons, protons, alpha, beta and/or gamma particles.

Radiation-induced grafting of acrylic acid onto other polymer films is disclosed by Gazard, M. et al., "Lithographic Technique Using Radiation-Induced Grafting of Acrylic Acid Into Poly(Methyl Methacrylate) Films," *Polymer Engineering and Science*, 20:16 (1980). Gazard et al. disclose that, under ionizing radiation, polymers undergo changes in their properties, especially in their solubility. Ionizing radiation of polymers leads to the formation of free radicals and other intermediates, which may be used to initiate the grafting of a monomer to produce a grafted copolymer with properties different from those of the initial polymer. For example, irradiated PMMA, onto which acrylic acid is grafted produces a graft copolymer which is insoluble in the solvents of PMMA.

U.S. Pat. No. 2,999,056 also discloses that an unsaturated organic acid may be attached to a shaped polymeric structure by ionizing radiation.

Other methods of altering the surface of polymeric objects include exposing the surface of a polymeric article to low temperature plasma or an electrically charged gaseous atmosphere, followed by contacting the surface of the polymeric article with a surface modifying compound as described, for example, in U.S. Pat. No. 4,344,981. This two-step method is generally called plasma-induced coating. Plasma induction has been described generally in U.S. Pat. No. 4,328,257, Yasuda, "Plasma for Modification of Polymers," *J. Macromol. Sci. C. Chem.*, a 10(3):383 (1978), Mittal, "Interfacial Chemistry and Adhesion: Recent Developments and Prospects," *Pure & Appl. Chem.*, 52:1295 (1980), Akovali, G. and Hasirci, N., "Polymerization of Hexamethyldisiloxane by Plasma on Activated Charcoal: Investigation of Parameters," *J. Appl. Polymer Sci.*, 29:2617 (1984) and Liu, W. T. et al., "Polymethyl Methacrylate Resist Sensitivity Enhancement in X-Ray Lithography by *In Situ* Polymerization," *Appl. Phys. Lett.*, 44:973 (1984), for example.

Ionized vapor or plasma discharge is typically created in a vacuum chamber in which the object to be modified is placed. The plasma discharge conditions the surface by creating free radicals and/or ions. It is known, for example, that exposing the surface of an object to plasma discharge, such as an oxygen plasma, enhances the wettability or hydrophilicity of such a surface. However, such treatment is only temporary. U.S. Pat. Nos. 3,925,178; 3,944,709; 4,072,769; 4,096,315; 4,122,942; 4,123,308; 4,131,691; 4,137,365; 4,214,014 and 4,478,873 disclose examples of polymers whose surface characteristics have been modified by a plasma discharge.

Plasma discharge treatment may also be used to prepare an object for the attachment or grafting of a compound or material to the plasma discharge treated object. For example, a plasma discharge step may be used to condition the surface for grafting by creating free

radicals to which a compound or material may be grafted. Such compounds or materials are generally called surface modifiers. Knight, P. M. et al., in "Surface Modification of Intraocular Lenses to Reduce Corneal Endothelial Damage," *Am. Intra-ocular Implants Soc. J.*, 5:123 (1979) disclose one example of a polymer object having a surface modifier attached thereto using gamma irradiation and radio frequency (RF) gas plasma treatment to generate free radicals on the surface of a PMMA intraocular lens followed by polymerizing hydrophilic monomers, in particular, HEMA and vinyl pyrrolidone, as a coating on the surface of the lens. While the coated surfaces exhibited enhanced hydrophilicity, the coated surfaces were not stable when boiled to sterilize them. Surface modification by gamma radiation followed by polymerization on the surface, on the other hand, remained intact through several hours of boiling. However, such coated PMMA surfaces were damaging to rabbit endothelial cells and surfaces coated with dissolvable coatings, such as polyvinyl acetate, were preferred.

Another example of a surface treated polymer is disclosed in U.S. Pat. No. 4,312,575. This patent discloses a soft, highly oxygen permeable, hydrophobic polymeric lens which has on its surface an ultra-thin, optically clear, permeable barrier coating which is the reaction product resulting from a glow discharge polymerization process conducted in a hydrocarbon or halogenated hydrocarbon gaseous atmosphere. While the plasma discharge process, itself, results in a hydrophilic surface, subsequent exposure to a glow discharge atmosphere of oxygen or ambient oxygen yields a still more hydrophilic surface.

U.S. Pat. No. 4,409,258 discloses a method for rendering contact lenses hydrophilic by bombarding the lens, which may be PMMA or silicone, with a positive ion beam generated by a plasma discharge, such as an oxygen plasma. The lens is thereafter hydrated, preferably at an elevated temperature.

Examples of surface treated polymeric lenses for use in humans are included in U.S. Pat. No. 3,880,818. This patent discloses a soft contact lens that is flexible and physiologically compatible, which is made by manufacturing a hard, inflexible prepolymer, such as a hard acrylic acid-type polymer, and reacting the inflexible prepolymer with an alcohol to esterify pendent carboxyl groups with alkyl groups, hydroxy alkyl groups or alkoxyalkyl groups, containing no more than eleven carbon atoms.

U.S. Pat. No. 4,143,949 discloses a discharge polymerization and coating process for making a hydrophilic contact lens from an oxygen permeable, hydrophobic polymer. The hydrophobic lens is placed in a glow discharge apparatus containing an atmosphere comprising a polymerizable organic monomer, such as hydroxyalkyl acrylate or methacrylate, glycidyl methacrylate, propylene oxide or N-vinyl-2-pyrrolidone, where the glow discharge is used to polymerize the monomer onto the surface of the contact lens.

Other examples of surface treated polymeric objects include U.S. Pat. Nos. 3,228,741; 3,925,178; 3,959,105; 3,985,697; 4,055,378; 4,277,595; 4,405,773; 4,430,458; 4,463,148; and 4,731,080. U.S. Pat. No. 4,731,080, for example, discloses a coated intraocular lens having a hydrophobic cross-linked vinyl-containing silicone polymer placed on the lens surface in solution.

It would be desirable to have a biocompatible, surface modified material and a method for producing the same, where the surface modification is substantially permanent, results in a smooth surface on the cellular level and where the surface modified material may be used, inter alia, as a prosthetic device in mammals.

BRIEF SUMMARY OF THE INVENTION

According to the present invention, a method of permanently modifying the surface of a substrate material so that the substrate material develops a microscopically smooth, biocompatible surface comprises covalently grafting at least a first biocompatible material having pendant terminal carboxylic acid or amine groups to the surface of the substrate material by radio frequency plasma-induced grafting. In addition, according to the present invention, a method of permanently modifying the surface of a substrate material further comprises cross-linking a second biocompatible material to the first biocompatible material grafted to the substrate material using a cross-linking agent.

In addition, the present invention is directed to a method of permanently modifying the surface of a substrate material so that the substrate material develops a microscopically smooth, biocompatible surface comprising covalently grafting a biocompatible, hydrophilic or hydrophobic material to the surface of the substrate material by radio frequency plasma-induced grafting.

Further, the present invention is directed to a prosthesis used in mammals comprising a polymer substrate or core and at least a first biocompatible material grafted to the polymer core by plasma induction.

In addition, a prosthesis used in mammals further comprises a polymer core, a first biocompatible material having pendant terminal carboxylic acid or amine groups covalently grafted to the polymer core by plasma induction and a second biocompatible material cross-linked to the grafted first biocompatible material by a cross-linking agent.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Although the methods of preparation of the invention apply generally to the preparation of permanent surface modification of many different materials, the methods are described and exemplified below with specific examples using polymeric intraocular lenses as prostheses which may be used in mammals. It will be understood by one skilled in the art that the methods of the present invention may be used to prepare permanently modified surfaces of other substrate materials, such as those prosthestic materials identified above. Moreover, it will be apparent to one skilled in the art that the methods of the present invention readily lend themselves to the preparation of materials having modified or enhanced surface characteristics having other uses.

According to the present invention, a first biocompatible material having pendant terminal carboxylic acid or amine groups is covalently grafted to the surface of a substrate material by radio frequency plasma induction. Examples of substrate materials to which a biocompatible material may be grafted include polymers, such as silicone, polypropylene, polyester, polytetrafluoroethylene, polyurethane, HEMA and PMMA.

Generally, the substrate material used in accordance with the present invention is chosen dependent upon its intended use. For example, PMMA and HEMA are two materials of choice for use in prosthetic devices intended for implantation or other application in mammals. However, in view of the present specification, one

skilled in the art will appreciate that any organic polymer may be used as a substrate material, as well as certain ceramics and metals. Where an optically clear polymer for use in prosthetic devices for mammals is the substrate material, it is presently preferred that the polymer comprises PMMA.

The surface properties of the substrate material (viz: hydrophobic for PMMA, for example) are modified by grafting a first biocompatible material having pendant terminal carboxylic acid or amine groups to the surface thereof. Once the substrate material surface has been modified by covalently grafting the biocompatible material to the surface of the substrate material, the modified surface should have properties which are relatively nontoxic and nonirritating to living tissues. In addition, the modified surface should not adversely affect the desired properties of the remainder of the substrate material, such as structural integrity and optical clarity, among others. In addition, the modified surface should be microscopically smooth. As used herein, the term "microscopically smooth" shall mean that the surface of the modified substrate should be featureless upon examination at an enlargement of about 10,000 x. Further, the modified surface should be absent of crystallinity, cross-linked and thermally stable. Further, surface modification of a substrate material in accordance with the present invention should result in a substrate material which exhibits a reduced contact angle or wettability of the polymer surface of less than about 30° to about 50°.

Where the substrate material is intended for use in or as a prosthetic device, such as an intraocular lens, the surface modification of the present invention should not adversely affect the transparency or ocular acuity of the substrate material. Further, the first biocompatible material to be grafted to the substrate surface preferably comprises a material that is relatively easy to polymerize in a gas plasma environment. Such materials include unsaturated compounds or those compounds containing nitrogen, silicone or halogen. Materials that are relatively difficult to polymerize in a gas plasma environment include saturated compounds, cyclic compounds, compounds with a high molecular weight, such as proteins, and those compounds containing oxygen.

Preferably, the first biocompatible material having pendant terminal carboxylic acid or amine groups comprises ethylenediamine, polyacrylic acid, allylamine and/or diethylenetriamine. In one embodiment of the present invention where the substrate material is intended for use as an intraocular lens, it is presently preferred that the first biocompatible material comprises acrylic acid (which polymerizes to polyacrylic acid [PAA] under plasma treatment). One skilled in the art will appreciate, however, that other suitable biocompatible materials having the properties described above may be used in accordance with the present invention.

The first biocompatible material should be grafted to the substrate material in a relatively uniform thickness and texture along the surface of the substrate material. In addition, especially where it is desired to use the substrate material as a prosthetic lens, it is preferred that the first biocompatible material is present on the surface of the substrate material in a relatively small thickness to prevent interference with the optical clarity of the lens. More preferably, the first biocompatible material is present in a monomolecular layer. In one embodiment of the present invention, for example, a surface modified substrate comprises a first biocompatible material grafted to the surface of a substrate material with a biocompatible material thickness of about 100 A.

Grafting of the first biocompatible material according to the present invention is conducted using radio frequency plasma-induced grafting. Other methods of grafting, such as electronic or ultra-violet (UV) radiation are not suitable where it is desired (as it is here) to modify only the surface of the polymer material. For example, where a prosthetic lens, such as a contact lens or intraocular lens, is desired to be modified, modification should be confined to the surface of the lens to avoid affecting the optical properties of the lens. Radio frequency plasma-induced grafting according to the present invention avoids structural modification below the outer-most surface layer, and generally results in more desirable optical properties.

Such gas plasma-induced grafting may be conducted in a radio frequency gas plasma reactor capable of generating a frequency of about 1 MHz to about 40 MHz. The frequency generated by a typical commercial gas plasma reactor is about 13.56 MHz, although one skilled in the art will recognize that higher and lower frequencies may be used to graft the biocompatible material to the surface of the substrate material in a radio frequency gas plasma reactor, depending on the substrate material and biocompatible material used, the relative ease or difficulty in preparing the surface of the substrate material for grafting, the relative ease or difficulty of vaporizing or polymerizing the biocompatible material, among other factors.

The first step of radio frequency plasma treatment according to this invention is the removal or etching of material from the surface of the substrate material being bombarded by the plasma. This process cleans the substrate and produces active species on the surface so treated, such as ions and free radicals, which can be used for inducing a graft reaction.

Generally, the rate of material removal may be controlled relative to the rate of deposition of a graft polymer by the frequency of the gas plasma, the power of the gas plasma, the treatment time, the gas used in the plasma, the gas pressure/concentration, and the type of bond desired on the treated substrate material surface, depending on the particular substrate material.

Plasma-induced grafting of the first biocompatible material to the substrate material may be conducted in radio frequency plasma reactors known in the art. The Branson model 3003-1813 is one example of a suitable radio frequency gas plasma reactor which may be used to create a suitable gas plasma atmosphere in which a first biocompatible material having the properties described above may be vaporized and polymerized for grafting. One skilled in the art will appreciate, however, that other plasma reactors and apparatus may be used in accordance with the present invention.

Preferably, the ambient gas used in the radio frequency gas plasma-induced grafting is selected from the group consisting of nitrogen, ammonia and argon. More preferably, the gas used in the radio frequency gas plasma reaction is argon. Argon is an inert gas which creates active sites but does not produce new bonding when applied to a substrate surface in a RF gas plasma reactor. Oxygen, on the other hand, for example, tends to produce peroxides in such plasma-induced grafting reactions and is, therefore, generally less desired. One skilled in the art will understand, however, that other suitable gases may be used in the plasma reaction in accordance with the present invention.

Surface modification by plasma-induced grafting in accordance with the present invention essentially comprises two steps: (1) plasma treatment or preparation of the substrate surface; and (2) introduction of the monomer of the first biocompatible material into the plasma where the monomer becomes grafted to the substrate surface. As discussed above, the plasma treatment of the substrate surface breaks surface bonds, generating ions and free radicals at the surface of the substrate material, thus "activating" the surface. Introduction of the monomer into the radio frequency induced plasma causes the monomer to react with the substrate surface, polymerize and become grafted to the substrate surface.

The length of time the first biocompatible material in an induced plasma state should be allowed to react with the substrate material depends upon several factors, including the plasma or radiation power, the radio frequency, the flow concentration or pressure, the temperature and the desired thickness of the grafted material. Preferably, the radiation power is about 10 watts to about 200 watts, depending upon the biocompatible material. For example, where the biocompatible material comprises silazane, hexamethyldisiloxane, NVP (discussed below) or PAA, it is presently preferred that the radiation power is about 50 watts. Where the biocompatible layer material comprises HEMA (discussed below), it is presently preferred that the radiation power is about 10 watts to about 100 watts. In any event, the reactor power used and the duration such power is used should be low and/or short enough so as to not induce thermal circulation and melt the substrate material. For example, where the substrate material comprises PMMA, the reaction conditions (i.e., power and duration) should not increase the temperature of the substrate material above about 40°–45° C. One skilled in the art may readily determine, in view of the plasma reaction variables described above, the desired plasma radiation power to be used in accordance with the present invention.

The plasma reaction is preferably conducted for a period of time of about 1 minute to about 30 minutes. More preferably, the plasma reaction is allowed to occur for a period of time of about 1 minutes to about 30 minutes. The flow concentration or vapor pressure of the plasma reactants in the reactor chamber should be low enough so that the particular monomer of the biocompatible material vaporizes when introduced into the reactor. Preferably, the vapor pressure is about 0.1 torr to about 0.6 torr. More preferably, the vapor pressure is about 0.4 torr.

The temperature in the plasma reaction should not be allowed to approach those temperatures which may damage the substrate material or the biocompatible material. High radiation power and any polymerization reaction (i.e., polymerization which may occur when the grafting reaction occurs; e.g.: polymerization to polyacrylic acid) tend to increase the temperature of the plasma reaction. It is desirable, therefore, to maintain the temperature in the plasma reaction below the temperature at which the substrate material and/or the graft material will be damaged, typically below about 40°–50° C.

In view of this disclosure, one skilled in the art may readily determine the reactants, time, pressure and temperature conditions for a reaction using given materials without undue experimentation. For example, in one embodiment of the present invention, liquid acrylic acid liquid is introduced into a plasma reactor chamber having a plasma-etched or treated body of PMMA where, because of the low pressure within the chamber, the acrylic acid vaporizes. The acrylic acid is exposed to 50 watts of radio frequency radiation at about 27.5° C. at a reactant or vapor pressure of about 0.4 torr.

In addition to the first biocompatible materials discussed above, it may be desired to use other materials which do not have pendant terminal carboxylic acid or amine groups but which exhibit good biocompatibility and exhibit the desired characteristics described above for the first biocompatible materials (i.e., not adversely affecting substrate, relatively easy to polymerize, etc.). Examples of such biocompatible materials include the hydrophobic materials hexamethyldisiloxane, silazane, and/or N-vinyl pyrrolidone (NVP) and the hydrophilic material HEMA, although one skilled in the art will recognize that other materials having the desired properties discussed above may be used in accordance with this invention. The method and materials for grafting such other biocompatible materials to a substrate material are the same as those radio frequency plasma-induced grafting methods and materials described above. However, where biocompatible materials which do not have pendant carboxylic acid or amine groups are used in accordance with this invention, further surface modification by cross-linking a second biocompatible material to the grafted material (discussed below) is unavailable.

Although not necessary, it may be desired in accordance with the present invention to further modify the surface of a substrate material by cross-linking a second biocompatible material to the grafted first biocompatible material. One skilled in the art will recognize, for example, that where PAA is grafted to the surface of a substrate material, pendant terminal carboxylic acid groups are available to react, particularly via a cross-linking agent, with a second biocompatible material. Where the grafted first biocompatible material comprises ethylenediamine or allylamine, for example, pendant amine groups are available to react with a second biocompatible material.

The post-plasma cross-linking of a second biocompatible material to the grafted first biocompatible material preferably occurs in a buffered solution where the cross-linking reaction may occur for several minutes to several hours and typically about 24 hours. Preferably, the buffer solution comprises an aqueous solution of sodium bicarbonate or acetic acid having a pH of about 3.

The second biocompatible material should be reactive with the cross-linking agent and, depending upon the intended use of the substrate material, should be chemically stable, nontoxic and non-irritating.

Preferably, the second biocompatible material comprises a polysaccharide, such as hyaluronic acid, hyaluronate, heparin, agarose or chondroitin sulfate. It is presently preferred that the second biocompatible material comprises chondroitin sulfate. One skilled in the art will recognize, however, that the second biocompatible material may comprise other chemicals and drugs, which may be cross-linked to the grafted first biocompatible material using a cross-linking agent in accordance with the present invention. It is believed that examples of suitable chemicals or drugs include methotrexate and other antimetabolic agents and immunosuppressors.

The cross-linking agent must be capable of attaching (cross-linking) the second biocompatible material to the

pendant amine or carboxylic acid groups on the grafted first biocompatible material and must be incorporated into the first and second biocompatible cross-linked materials. The cross-linking agent, especially once incorporated into the cross-linked first and second biocompatible materials, should not adversely affect the biocompatibility of the modified surface of the substrate material and should not adversely affect the characteristics of the substrate material, the grafted first biocompatible material or the cross-linked second biocompatible material. Preferable cross-linking agents in accordance with the present invention include glutaraldehyde, bis(3,5-dibromosalicyl)fumarate, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and carbodiimide

In one embodiment of the present invention, the surface modified substrate material (i.e., the substrate material having a first biocompatible material grafted thereto), the cross-linking agent and the second biocompatible material are combined in a neutral buffer solution (pH about 7), where cross-linking to the surface modified substrate can occur.

In another embodiment of the present invention, the cross-linking agent and the second biocompatible material are mixed together prior to the addition of the surface modified substrate in a buffer solution, such as those buffer solutions described above.

Where it is desired to further modify the surface of a substrate by cross-linking a second biocompatible material to the grafted material in accordance with the present invention, the substrate having its surface modified by plasma-induced grafting should be relatively free from any excess reagents used during the grafting process. Generally, excess reagents may be removed by rinsing the surface modified substrate in distilled water.

Where the first biocompatible material is hydrophilic, the surface modified substrate material should exhibit a greater hydrophilicity than the untreated substrate material. Hydrophilicity may be measured by wettability or contact angle. Wettability or surface energy is related to surface tension and is measured in dyne/cm, which is easily conducted by submerging a testing surface into a solvent and removing the testing surface from the solvent. The more and faster the solvent beads up on the surface of the substrate, as determined by the diameter and volume of the beads or drops, the higher the wettability value.

The contact angle of a substrate is that angle formed when a drop of liquid is placed on the surface of the substrate and may be measured with a goniometer. Where the intended use of the substrate is in an aqueous environment, water is the preferred liquid. If the drop of liquid on the surface of the substrate is relatively flat, the substrate may be said to be hydrophilic and the contact angle is relatively low (i.e., about 5°–30°). Conversely, if the liquid drop is relatively beadlike, the substrate may be said to be less hydrophilic and has a relatively higher contact angle (i.e., about 70°–110°). For example, the contact angle of untreated PMMA is about 77°. The contact angle of PMMA treated in accordance with the present invention with: (1) an argon gas plasma is about 45° to about 65°; (2) a polyacrylic acid graft is about 45° to about 55°; (3) oxygen gas plasma treatment subsequent to grafting is about 30° to about 55°; (4) an allylamine graft is about 30° to about 40°; and (5) CDS cross-linked to the PAA graft is about 10° to about 15°. Preferably, the contact angle of a material for use in or as a prosthetic device is about 45° or less and more preferably, about 15° or less.

Novel products having a permanently modified surface resulting from the method of the present invention described above include prostheses for use in mammals comprising a polymer substrate or core and a biocompatible material grafted thereto. For example, one presently preferred prosthesis for use in mammals comprises a PMMA core having a modified surface comprising PAA substantially permanently grafted to the PMMA surface.

In addition, novel products having a permanently modified surface using the method of the present invention include prostheses used in mammals comprising a polymer core, a first biocompatible material grafted thereto and a second biocompatible material cross-linked to the grafted coating by a cross-linking agent. In one embodiment of the present invention, for example, a prosthesis used in mammals comprises a PMMA core, having a modified surface comprising PAA grafted to the PMMA surface and chondroitin sulfate cross-linked to the PAA using glutaraldehyde as the cross-linking agent.

Other novel products produced using the method of the present invention include an intraocular lens having a permanently modified, biocompatible surface, which comprises a polymer lens body, such as PMMA, a first biocompatible material having pendant carboxylic acid or amine groups, such as PAA or ethylenediamine grafted to the surface of the lens body, and a second biocompatible material, such as chondroitin sulfate cross-linked to the grafted first biocompatible material via a cross-linking agent, such as glutaraldehyde.

The invention will now be illustrated in further detail by reference to the following specific, non-limiting examples.

EXAMPLE 1

An intraocular lens manufactured by CILCO (J-FLEX posterior chamber lens style SK-1) from PMMA was positioned in a Branson model 3003-1813 radio frequency gas plasma reactor. The pressure inside the reactor was reduced to less than about 0.10 torr and the surface of the lens was subjected to an argon gas (Ar) plasma at approximately 40° C. at 50 watts for 3 minutes. Acrylic acid vapor was introduced into the reactor and was allowed to react for 5 minutes at about 0.3 torr. Upon examination, the lens exhibited a uniform surface with a smooth texture and good biocompatibility in animal testing (no cellular or tissue remnant adhesion) with a contact angle of about 50°.

EXAMPLE 2

The procedures of Example 1 were followed, substituting ethylenediamine (EDAM) for acrylic acid. The resulting lens coating had a contact angle of 35°–45° and exhibited a smooth microstructure upon SEM analysis.

EXAMPLE 3

The coated lens prepared in Example 2 was placed in a vessel containing 2ml (25% solution) glutaraldehyde, 1.5 g chondroitin sulfate, 1 ml (25% solution) polyacrylic acid and acetic acid sufficient to adjust pH to about 3 (3-4ml). The mixture was brought to 100 ml by addition of distilled water. The mixture was allowed to incubate at room temperature for 24 hours, rinsed with distilled water and dried. Scanning electron micrograph examination of the lens indicated that the surface had a

thick film having a very coarse texture. The water contact angle was less than about 10°-15°, indicating that chondroitin sulfate had attached to the surface. The dry lens had a hazy appearance which disappeared upon immersion in water. Lens clarity and acuity was not significantly altered, as confirmed by spectroscopic measurements.

EXAMPLE 4

Following the procedures of Example 3 a series of intraocular lenses were treated. Table 1 indicates the steps and/or materials used or present (indicated by a "Y") for each run and the resulting contact angles for each lens.

TABLE 1

Run	Ar	EDAM	Buffer (8.4)	PAA	GDA (.5%)	CDS/GDA (.05%)	CDS/GDA (.1%)	Rinse (4° C.)	Contact Angle (F/A)
1	Y	Y	Y	Y	Y	Y		Y	39/44
2	Y	Y	Y	Y	Y		Y	Y	31/35
3	Y	Y	Y		Y	Y		Y	42/53
4	Y	Y	Y		Y		Y	Y	42/51
5	Y	Y	Y/3		Y	Y		Y	35/40

F = freshly prepared lens
A = aged lens
Y = present or conducted

EXAMPLE 5

An intraocular lens manufactured by CILCO from PMMA as in Example 1 was placed in a Branson model 3003-1813 radio frequency gas plasma reactor. The pressure within the reactor was reduced to about 0.1 torr and an argon gas plasma was created using about 50 watts radio frequency at 40° C. The plasma reaction was allowed to proceed for about 5 minutes. The contact angle of the non-treated PMMA intraocular lens was about 70. and the contact angle of the argon plasma treated lens was about 45°. The lens was put back in the reactor and vapor acrylic acid was introduced into the chamber. The pressure was reduced to about 0.3 torr and a portion of the acrylic acid was ionized using 50 watts. The plasma reaction was allowed to continue for 5 minutes. The contact angle of the acrylic acid modified surface (polyacrylic acid graft) treated lens was about 35°. The lens was placed back into the reactor and treated with an oxygen gas plasma using 50 watts at about 0.2 torr for 1-3 minutes. The contact angle of the lens after oxygen plasma treatment was about 30°.

EXAMPLE 6

The lens prepared in Example 5 was placed in a sodium bicarbonate buffer solution to which was added 9mg EDC and allowed to react for 120 minutes at 37° C. In a second vessel, 1.5 g chondroitin sulfate and 0.1 g EDC were mixed in distilled water for 120 minutes at 37° C. The chondroitin sulfate/EDC mixture was added to the lens solution and allowed to react for 24 hours.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than the specification, as indicating the scope of the invention.

We claim:

1. A method of permanently modifying the surface of a substrate material to produce a microscopically smooth, biocompatible surface thereon, comprising covalently grafting a polymeric, first biocompatible material to the surface of the substrate material by radio frequency plasma induction, the biocompatible material having pendant terminal carboxylic acid or amine groups.

2. The method according to claim 1, wherein the grafting is induced in a radio frequency plasma reactor generating a frequency of about 1 MHz to about 40 MHz.

3. The method according to claim 2, wherein the frequency is about 13.56 MHz.

4. The method according to claim 2, wherein gas is present in the reactor, said gas being selected from the group consisting of nitrogen, ammonia and argon.

5. The method according to claim 4, wherein the gas is argon.

6. The method according to claim 1, wherein the first biocompatible material comprises ethylenediamine, polyacrylic acid, diethylenetriamine or allylamine.

7. The method according to claim 1, wherein the substrate material is selected from the group consisting of silicone, polypropylene, polyester, polytetrafluoroethylene, polyurethane, hydroxyethylmethacrylate and polymethyl-methacrylate.

8. The method according to claim 1, lo wherein the surface of the substrate material is further modified by covalently cross-linking a second biocompatible material to the grafted first biocompatible material using a cross-linking agent.

9. The method according to claim 8, wherein the cross-linking agent is applied to the substrate material surface prior to the application of the second biocompatible material.

10. The method according to claim 8, wherein the second biocompatible material comprises a polysaccharide.

11. The method according to claim 10, wherein the polysaccharide is selected from the group consisting of hyaluronic acid, hyaluronate, agarose and chondroitin sulfate.

12. The method according to claim 10, wherein the polysaccharide is chrondroitin sulfate.

13. The method according to claim 8, wherein the cross-linking agent is selected from the group consisting of glutaraldehyde, bis(3,5-dibromosalicyl)fumarate, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide and carbodiimide.

14. The method according to claim 8, wherein the cross-linking agent is glutaraldehyde.

15. The method according to claim 8, wherein the substrate material is rinsed with distilled water prior to cross-linking the second biocompatible material to the grafted first biocompatible material.

16. The method according to claim 8, wherein the cross-linking occurs in the presence of a neutral buffer solution.

17. The method according to claim 1, wherein said first biocompatible material is polyacrylic acid, said substrate is a polymethylmethacrylate substrate, said grafting is induced by argon gas plasma at a frequency of about 13.56 MHz, and after said grafting, said substrate is rinsed with distilled water, and glutaraldehyde and chondroitin sulfate are applied sequentially in a neutral buffer solution to said polyacrylic acid grafted to said polymethylmethacrylate substrate.

18. The method according to claim 1, wherein, prior to radio frequency plasma induction, the first biocompatible material is a monomer.

19. The method according to claim 18, wherein the monomer of the first biocompatible material is selected from the group consisting of the monomers of ethylenediamine, polyacrylic acid, diethylenetriamine and allylamine.

20. A method of permanently modifying the surface of a substrate material to produce a microscopically smooth, biocompatible surface thereon, comprising covalently grafting a biocompatible, hydrophilic polymeric material to the surface of the substrate material by radio frequency plasma induction.

21. The method according to claim 20, wherein the biocompatible, hydrophilic polymeric material comprises ethylenediamine, polyacrylic acid, hydroxyethylmethacrylate, diethylenetriamine or allylamine.

22. A method of permanently modifying the surface of a substrate material to produce a microscopically smooth, biocompatible surface thereon, comprising covalently grafting a biocompatible, hydrophobic polymeric material to the surface of the substrate material by radio frequency plasma induction.

23. The method according to claim 22, wherein the biocompatible, hydrophobic material comprises N-vinylpyrrolidone, silazane and hexamethyldisiloxane.

* * * * *

EXHIBIT C

US005260093A

United States Patent [19]

Kamel et al.

[11] Patent Number: 5,260,093

[45] Date of Patent: * Nov. 9, 1993

[54] METHOD OF MAKING BIOCOMPATIBLE, SURFACE MODIFIED MATERIALS

[75] Inventors: Ihab Kamel, Drexel Hill; David B. Soll, Rydal, both of Pa.

[73] Assignees: Drexel University; Ophthalmic Research Corporation, both of Philadelphia, Pa.

[*] Notice: The portion of the term of this patent subsequent to Jan. 14, 2009 has been disclaimed.

[21] Appl. No.: 820,169

[22] Filed: Jan. 13, 1992

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 342,270, Apr. 24, 1989, Pat. No. 5,080,924.

[51] Int. Cl.[5] A01N 1/02

[52] U.S. Cl. 427/2; 427/164; 427/489; 427/490; 427/491; 427/509; 427/515; 427/520; 623/6; 623/901; 264/25

[58] Field of Search ..... 427/2, 40, 41, 45.1, 427/385.5, 387, 164, 489, 490, 491, 508, 509, 515, 520, 536; 623/6, 16 G, 901; 523/105, 106, 112, 113; 204/165; 264/25; 351/160 H, 160 R

[56] References Cited

U.S. PATENT DOCUMENTS

2,999,056	9/1961	Tanner	522/118
3,228,741	1/1966	Becker	351/160 R
3,880,818	4/1975	Shen et al.	526/322
3,925,178	12/1975	Gesser et al.	204/165
3,944,709	3/1976	Levy	428/409
3,959,105	5/1976	Feneberg et al.	204/165
3,961,379	6/1976	Highgate	522/116
3,985,697	10/1976	Urbach	523/106
4,055,378	10/1977	Feneberg et al.	204/165
4,055,378	10/1977	Feneberg et al.	351/160 R
4,072,769	2/1978	Lidel	427/38
4,096,315	6/1978	Kubacki	428/412

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

58-216222	12/1983	Japan	427/489
2119957	11/1983	United Kingdom	351/160 R

OTHER PUBLICATIONS

H. Yasuda, "Plasma for Modification of Polymers," *J. Macromol. Sci.-Chem.*, A10(3), pp. 383–420 (1976).

Knight et al., "Surface Modification of Intraocular Lenses to Reduce Corneal Endothelial Damage," *AM Intra-Ocular Implant Soc. J*-vol. V, pp. 123–130, Apr. 1979.

Gazard et al., "Lithographic Technique Using Radiation-Induced Grafting of Acrylic Acid into Poly(-Methyl Methacrylate) Films," *Polymer Engineering and Science*, vol. 20, No. 16, pp. 1069–1072 (1980).

K. L. Mittal, "Interfacial Chemistry and Adhesion: Recent Developments and Prospects," *Pure & Appl. Chem.*, vol. 52, pp. 1295–1305 (1980).

Akovali et al., "Polymerization of Hexamethyldisiloxane by Plasma on Activated Charcoal: Investigation of

(List continued on next page.)

Primary Examiner—Terry J. Owens

Attorney, Agent, or Firm—Panitch Schwarze Jacobs & Nadel

[57] ABSTRACT

A method of permanently modifying the surface of a substrate material so as to develop a microscopically smooth, biocompatible surface thereon comprises covalently grafting a biocompatible polymeric material to the surface of the substrate material by radio frequency plasma-induced grafting. The biocompatible polymeric material is preferably the same as the substrate material. In addition, a method of permanently modifying the surface of a substrate material comprises subjecting the substrate surface to radio frequency plasma sufficient to raise the temperature at the substrate material to just above the glass transition temperature (T_g) of the substrate material for a time sufficient to produce a microscopically smooth, biocompatible surface on the substrate material. Further, a prosthesis used in mammals, including an intraocular lens, comprises a polymeric material core and a biocompatible polymeric material covalently grafted to the polymer core by radio frequency plasma induction.

13 Claims, No Drawings

FOREIGN PATENT DOCUMENTS

4,099,859	7/1978	Merrill	351/160 H
4,122,942	10/1978	Wolfson	206/5.1
4,123,308	10/1978	Nowlin et al.	427/41
4,131,691	12/1978	Morley et al.	427/41
4,137,365	1/1979	Wydeven et al.	428/412
4,143,949	3/1979	Chen	427/41
4,189,364	2/1980	Action et al.	522/4
4,214,014	7/1980	Hofer et al.	427/40
4,240,163	12/1980	Galin	623/6
4,277,595	7/1981	Deichert et al.	528/26
4,311,828	1/1982	Imada et al.	204/165
4,312,575	1/1982	Peyman et al.	351/160 H
4,328,257	5/1982	Muehlberger et al.	427/34
4,344,981	8/1982	Imada et al.	427/40
4,405,773	9/1983	Loshaek et al.	526/318.42
4,409,258	10/1983	Feurer et al.	427/38
4,430,458	2/1984	Tighe et al.	523/108
4,463,148	7/1984	Hofer et al.	526/264
4,478,873	10/1984	Masso et al.	427/40
4,560,458	12/1985	Ueno et al.	204/165
4,632,842	12/1986	Karwoski et al.	427/2
4,656,083	4/1987	Hoffman et al.	427/41
4,718,907	1/1988	Karwoski et al.	427/2
4,720,512	1/1988	Hu et al.	523/112
4,731,080	3/1988	Galin	623/6
4,865,870	9/1989	Hu et al.	427/2
4,885,077	12/1989	Karakelle et al.	427/41
4,919,659	4/1990	Horbett et al.	427/2
4,927,676	5/1990	Williams et al.	427/2
5,080,924	1/1992	Kamel et al.	427/164
5,091,204	2/1992	Ratner et al.	427/38

OTHER PUBLICATIONS

Parameters," *Journal of Applied Polymer Science*, vol. 29, pp. 2617–2625 (1984).

Liu et al., "Polymethyl Methacrylate Resist Sensitivity Enhancement in X-Ray Lithorgraph by In Situ Polymerization," *Appl. Phys. Lett.*, 44(10), pp. 973–975, May 15, 1984.

Keates et al., "Coated Intraocular Lenses," *Ophthalmic Surgery*, vol. 18, No. 9, pp. 693–697 (1987).

METHOD OF MAKING BIOCOMPATIBLE, SURFACE MODIFIED MATERIALS

CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation-in-part application of U.S. patent application Ser. No. 07/342,270, filed Apr. 24, 1989, now U.S. Pat. No. 5,080,924.

FIELD OF THE INVENTION

The present invention relates to methods of permanently modifying the surface of materials by plasma-induced and, where desired, post-plasma reactions to produce biocompatible, surface modified materials. In addition, the present invention relates to biocompatible, surface modified prostheses and, in particular, to a biocompatible, surface modified intraocular lens used in mammals.

BACKGROUND OF THE INVENTION

Prosthetic devices or prostheses are commonly used in medical procedures replacing or augmenting defective organs in mammals and humans, in particular, and are numerous and diverse in structure and application. Examples of prostheses include artificial joints, valve replacements, skin grafts, vascular grafts, shunts, plates and contact and intraocular lenses. Typically, prosthetic devices comprise natural and/or synthetic material which are abrasive on the cellular level. Various prostheses in current use or in experimental use comprise metals, ceramics, silicone rubbers, polyesters, polyurethanes and/or polysulfones. Synthetic polymers, such as polymethylmethacrylate (PMMA) and hydroxyethylmethacrylate (HEMA), for example, are preferred polymers for prosthetic use in general and contact lenses and intraocular lenses in particular.

PMMA, for example, has several beneficial characteristics for such prosthetic use, including excellent light transmission, good optical clarity, resistance to fluid diffusion and in vivo deterioration, ease in processing (injection molding or machining, for example) and ease in implantation, such as an intraocular lens, an artificial joint and other implantable prostheses.

Typical lens prostheses, for example, are manufactured by machining, which leaves circular lathe marks or grooves visible at even relatively low magnification. These machining remnants render the lens unusable until the surface is smoothed, typically by a mechanical polishing process. However, the conventional polishing process generally takes several days to complete, has a failure rate in excess of 30% and fails to produce a microscopically smooth surface.

Abrasive prostheses, especially those which are implanted, can cause tissue irritation, edema and scarring. For example, posterior lens capsule opacification is a prevalent problem among those patients who have received intraocular lens implants comprising conventionally polished PMMA and other similar materials.

It is desirable to modify the surface properties of such abrasive materials without changing the beneficial characteristics thereof by developing a smooth surface thereby discouraging tissue adhesion and inhibiting cellular growth. Prostheses which do not promote tissue adhesion and do not inhibit cellular growth and which are not otherwise toxic to living systems may be considered "biocompatible." Surface modification to develop a biocompatible surface should be resistant to

deterioration over time and should have no adverse effects on tissues and cells with which the surface modified material comes in contact.

Those skilled in the art have long recognized the need for biocompatible, surface modified materials for use in prosthetic devices and other materials. For example, U.S. Pat. No. 3,961,379 discloses a bioimplantable device manufactured from a cross-linked, swollen, hydrophilic polymer. These modified polymers must be solid and must be swellable by fluid swelling substances. Once swollen, the solid polymer is polymerized with a modifying substance by, for example, high energy particle radiation.

U.S. Pat. No. 4,189,364 discloses hydrophilic polymers formed in situ by irradiating a mixture of hydroxyalkyl methacrylate and a cross-linking agent. This patent discloses a process for forming hydrophilic polymer articles or hydrophilic polymer coatings on other substrates, such as glass or plastic, by polymerizing a hydrophilic monomer system by high energy particulate irradiation, such as accelerated electrons or nuclear particles including neutrons, protons, alpha, beta and/or gamma particles.

Radiation-induced grafting of acrylic acid onto other polymer films is disclosed by Gazard, M. et al., "Lithographic Technique Using Radiation-Induced Grafting of Acrylic Acid Into Poly(Methyl Methacrylate) Films," *Polymer Engineering and Science*, 20:16 (1980). Gazard et al. disclose that, under ionizing radiation, polymers undergo changes in their properties, especially in their solubility. Ionizing radiation of polymers leads to the formation of free radicals and other intermediates, which may be used to initiate the grafting of a monomer to produce a grafted copolymer with properties different from those of the initial polymer. For example, irradiated PMMA, onto which acrylic acid is grafted produces a graft copolymer which is insoluble in the solvents of PMMA.

U.S. Pat. No. 2,999,056 also discloses that an unsaturated organic acid may be attached to a shaped polymeric structure by ionizing radiation.

Other methods of altering the surface of polymeric objects include exposing the surface of a polymeric article to low temperature plasma or an electrically charged gaseous atmosphere, followed by contacting the surface of the polymeric article with a surface modifying compound as described, for example, in U.S. Pat. No. 4,344,981. This two-step method is generally called plasma-induced coating. Plasma induction has been described generally in U.S. Pat. No. 4,328,257, Yasuda, "Plasma for Modification of Polymers," *J. Macromol. Sci. C. Chem.*, 10(3):383 (1978), Mittal, "Interfacial Chemistry and Adhesion: Recent Developments and Prospects," *Pure & Appl. Chem.*, 52:1295 (1980), Akovali, G. and Hasirci, N., "Polymerization of Hexamethyldisiloxane by Plasma on Activated Charcoal: Investigation of Parameters," *J. Appl. Polymer Sci.*, 29:2617 (1984) and Liu, W. T. et al., "Polymethyl Methacrylate Resist Sensitivity Enhancement in X-Ray Lithography by In Situ Polymerization," *Appl. Phys. Lett.*, 44:973 (1984), for example.

Ionized vapor or plasma discharge is typically created in a vacuum chamber in which the object to be modified is placed. The plasma discharge conditions the surface by creating free radicals and/or ions. It is known; for example, that exposing the surface of an object to plasma discharge, such as an oxygen plasma,

enhances the wettability or hydrophilicity of such a surface. However, such treatment is only temporary. U.S. Pat. Nos. 3,925,178; 3,944,709; 4,072,769; 4,096,315; 4,122,942; 4,123,308; 4,131,691; 4,137,365; 4,214,014 and 4,478,873 disclose examples of polymers whose surface characteristics have been modified by a plasma discharge.

Plasma discharge treatment may also be used to prepare an object for the attachment or grafting of a compound or material to the plasma discharge treated object. For example, a plasma discharge step may be used to condition the surface for grafting by creating free radicals to which a compound or material may be grafted. Such compounds or materials are generally called surface modifiers. Knight, P. M. et al., in "Surface Modification of Intraocular Lenses to Reduce Corneal Endothelial Damage," *Am. Intra-ocular Implants Soc. J.*, 5:123 (1979) disclose one example of a polymer object having a surface modifier attached thereto using gamma irradiation and radio frequency (RF) gas plasma treatment to generate free radicals on the surface of a PMMA intraocular lens followed by polymerizing hydrophilic monomers, in particular, HEMA and vinyl pyrrolidone, as a coating on the surface of the lens. While the coated surfaces exhibited enhanced hydrophilicity, the coated surfaces were not stable when boiled to sterilize them. Surface modification by gamma radiation followed by polymerization on the surface, on the other hand, remained intact through several hours of boiling. However, such coated PMMA surfaces were damaging to rabbit endothelial cells and surfaces coated with dissolvable coatings, such as polyvinyl acetate, were preferred.

Another example of a surface treated polymer is disclosed in U.S. Pat. No. 4,312,575. This patent discloses a soft, highly oxygen permeable, hydrophobic polymeric lens which has on its surface an ultra-thin, optically clear, permeable barrier coating which is the reaction product resulting from a glow discharge polymerization process conducted in a hydrocarbon or halogenated hydrocarbon gaseous atmosphere. While the plasma discharge process, itself, results in a hydrophilic surface, subsequent exposure to a glow discharge atmosphere of oxygen or ambient oxygen yields a still more hydrophilic surface.

U.S. Pat. No. 4,409,258 discloses a method for rendering contact lenses hydrophilic by bombarding the lens, which may be PMMA or silicone, with a positive ion beam generated by a plasma discharge, such as an oxygen plasma. The lens is thereafter hydrated, preferably at an elevated temperature.

Examples of surface treated polymeric lenses for use in humans are included in U.S. Pat. No. 3,880,818. This patent discloses a soft contact lens that is flexible and physiologically compatible, which is made by manufacturing a hard, inflexible prepolymer, such as a hard acrylic acid-type polymer, and reacting the inflexible prepolymer with an alcohol to esterify pendant carboxyl groups with alkyl groups, hydroxy alkyl groups or alkoxyalkyl groups, containing no more than eleven carbon atoms.

U.S. Pat. No. 4,143,949 discloses a discharge polymerization and coating process for making a hydrophilic contact lens from an oxygen permeable, hydrophobic polymer. The hydrophobic lens is placed in a glow discharge apparatus containing an atmosphere comprising a polymerizable organic monomer, such as hydroxyalkyl acrylate or methacrylate, glycidyl methacrylate, propylene oxide or N-vinyl-2-pyrrolidone, where the glow discharge is used to polymerize the monomer onto the surface of the contact lens.

Other examples of surface treated polymeric objects include U.S. Pat. Nos. 3,228,741; 3,925,178; 3,959,105; 3,985,697; 4,055,378; 4,277,595; 4,405,773; 4,430,458; 4,463,148; and 4,731,080. U.S. Pat. No. 4,731,080, for example, discloses a coated intraocular lens having a hydrophobic cross-linked vinyl-containing silicone polymer placed on the lens surface in solution.

It would be desirable to have a biocompatible, surface modified material and a method for producing the same, where the surface modification is substantially permanent, results in a smooth surface on the cellular level and where the surface modified material may be used, inter alia, as a prosthetic device in mammals. One such method is disclosed in our co-pending U.S. patent application Ser. No. 07/342,270, filed Apr. 24, 1989, the disclosure of which is incorporated herein by reference.

BRIEF SUMMARY OF THE INVENTION

According to the present invention, a method of permanently modifying the surface of a polymeric substrate material so that the substrate material develops a microscopically smooth, biocompatible surface comprises covalently grafting a biocompatible polymeric material to the surface of the substrate material by radio frequency plasma-induced grafting where the biocompatible polymeric material comprises substantially the same material as the material forming the substrate.

In addition, the present invention is directed to a method of permanently modifying the surface of a substrate material so that the substrate material develops a microscopically smooth, biocompatible surface comprising subjecting the substrate surface to radio frequency plasma sufficient to etch the substrate surface and raise the temperature at the surface to a temperature just above the glass transition temperature (T_g) of the substrate material.

Further, the present invention is directed to a prosthesis used in mammals comprising a polymer substrate or core and a biocompatible polymeric material grafted to the polymer core by plasma induction, the biocompatible polymer material comprising substantially the same material as the material forming the substrate.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Although the methods of preparation of the invention apply generally to the preparation of permanent surface modification of many different materials, the methods are described and exemplified below with specific examples using polymeric intraocular lenses as prostheses which may be used in mammals. It will be understood by one skilled in the art that the methods of the present invention may be used to prepare permanently modified surfaces of other substrate materials, such as those prosthestic materials identified above. Moreover, it will be apparent to one skilled in the art that the methods of the present invention readily lend themselves to the preparation of materials having modified or enhanced surface characteristics having other uses.

According to one embodiment of the present invention, a biocompatible polymeric material is covalently grafted to the surface of a substrate material by radio frequency plasma induction. Examples of substrate materials to which a biocompatible material may be grafted include polymers, such as silicone, polypropyl-

ene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, PMMA, polyacrylic acid, or polymers of HEMA, ethylenediamine, diethylenetriamine, allylamine, hexamethyl-disiloxane, silazane and N-vinyl-pyrrolidone.

Generally, the substrate material used in accordance with the present invention is chosen dependent upon its intended use. For example, PMMA and HEMA are two materials of choice for use in prosthetic devices intended for implantation or other application in mammals. However, in view of the present specification, one skilled in the art will appreciate that any organic polymer may be used as a substrate material, as well as certain ceramics and metals. Where an optically clear polymer for use in prosthetic devices for mammals is the substrate material, it is presently preferred that the polymer comprises PMMA.

The surface of the substrate material is modified by grafting a biocompatible polymeric material to the surface thereof. In some cases where it is desired to have only one material present, the first biocompatible polymeric material is substantially the same as the material forming the substrate. Once the substrate material surface has been modified by covalently grafting the biocompatible material to the surface of the substrate material, the modified surface should have properties which are relatively nontoxic and nonirritating to living tissues. In addition, the modified surface should not adversely affect the desired properties of the remainder of the substrate material, such as structural integrity and optical clarity, among others. In addition, the modified surface should be microscopically smooth. As used herein, the term "microscopically smooth" shall mean that the surface of the modified substrate should be featureless upon examination at an enlargement of about 3,000 to about 10,000x. In addition, where desired and depending on the properties of the first biocompatible polymeric material, the modified surface should be absent crystallinity, cross-linked and thermally stable.

Where the substrate material is intended for use in or as a prosthetic device, such as an intraocular lens, the surface modification of the present invention should not adversely affect the transparency or ocular acuity of the substrate material. Further, the first biocompatible material to be grafted to the substrate surface preferably comprises a material that is relatively easy to polymerize in a gas plasma environment. Such materials include unsaturated compounds or those compounds containing nitrogen, silicone or halogen. Materials that are relatively difficult to polymerize in a gas plasma environment include saturated compounds, cyclic compounds, compounds with a high molecular weight, such as proteins, and those compounds containing oxygen.

Examples of presently preferred biocompatible polymeric material include polyacrylic acid, silicone, polypropylene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, polymethylmethacrylate or polymers of ethylenediamine, diethylenetriamine, allylamine or hydroxyethylmethacrylate.

The biocompatible polymeric material should be grafted to the substrate material in a relatively uniform thickness and texture along the surface of the substrate material. In addition, especially where it is desired to use the substrate material as a prosthetic lens, it is preferred that the biocompatible polymeric material is present on the surface of the substrate material in a relatively small thickness to prevent interference with the optical clarity of the lens. More preferably, the biocompatible polymeric material is present in a monomolecular layer. In one embodiment of the present invention, for example, a surface modified substrate comprises a biocompatible polymeric material grafted to the surface of a substrate material with a biocompatible polymeric material thickness of about 100 A.

Grafting of the biocompatible polymeric material according to the present invention is conducted using radio frequency plasma-induced grafting. Other methods of grafting, such as electronic or ultra-violet (UV) radiation are not suitable where it is desired (as it is here) to modify only the surface of the substrate material. For example, where a prosthetic lens, such as a contact lens or intraocular lens, is desired to be modified, modification should be confined to the surface of the lens to avoid affecting the optical properties of the lens. Radio frequency plasma-induced grafting according to the present invention avoids structural modification below the outer-most surface layer, and generally results in more desirable optical properties.

Such gas plasma-induced grafting may be conducted in a radio frequency gas plasma reactor capable of generating a frequency of about 1 MHz to about 40 MHz. The frequency generated by a typical commercial gas plasma reactor is about 13.56 MHz, although one skilled in the art will recognize that higher and lower frequencies may be used to graft the biocompatible polymeric material to the surface of the substrate material in a radio frequency gas plasma reactor, depending on the substrate material and biocompatible polymeric material used, the relative ease or difficulty in preparing the surface of the substrate material for grafting, the relative ease or difficulty of vaporizing or polymerizing the biocompatible material, among other factors.

The first step of radio frequency plasma treatment according to this invention is the removal or etching of material from the surface of the substrate material being bombarded by the plasma. This process cleans the substrate and produces active species on the surface so treated, such as ions and free radicals, which can be used for inducing a graft reaction.

Generally, the rate of material removal may be controlled relative to the rate of deposition of a graft polymer by the frequency of the gas plasma, the power of the gas plasma, the treatment time, the gas used in the plasma, the gas pressure/concentration, and the type of bond desired on the treated substrate material surface, depending on the particular substrate material.

Plasma-induced grafting of the biocompatible polymeric material to the substrate material may be conducted in radio frequency plasma reactors known in the art. The Branson model 3003-1813 is one example of a suitable radio frequency gas plasma reactor which may be used to create a suitable gas plasma atmosphere in which a first biocompatible material having the properties described above may be vaporized and polymerized for grafting. One skilled in the art will appreciate, however, that other plasma reactors and apparatus may be used in accordance with the present invention.

Preferably, the ambient gas used in the radio frequency gas plasma-induced grafting is selected from the group consisting of nitrogen, ammonia and argon and other noble gases. More preferably, the gas used in the radio frequency gas plasma reaction is argon. Argon is an inert gas which creates active sites but does not produce new bonding when applied to a substrate surface in a RF gas plasma reactor. Oxygen, on the other hand, for example, tends to produce peroxides in such

plasma-induced grafting reactions and is, therefore, generally less desired. Where no biocompatible material is to be grafted to the substrate surface (discussed below) or where the presence of reactive gas molecules on the substrate surface is not desired, it is presently preferred to use noble gas as ambient gas in the radio frequency gas plasma reactor, such as argon. One skilled in the art will be readily able to determine in view of this disclosure which suitable gases may be used in the plasma reaction in accordance with the present invention.

Surface modification by plasma-induced grafting in accordance with one embodiment of the present invention essentially comprises two steps: (1) plasma treatment or preparation of the substrate surface; and (2) introduction of the monomer of the biocompatible polymeric material into the plasma where the monomer becomes grafted to the substrate surface. As discussed above, the plasma treatment of the substrate surface breaks surface bonds, generating ions and free radicals at the surface of the substrate material, thus "activating" the surface. Introduction of the monomer into the radio frequency induced plasma causes the monomer to react with the substrate surface, polymerize and become grafted to the substrate surface.

The length of time the biocompatible material in an induced plasma state should be allowed to react with the substrate material depends upon several factors, including the plasma or radiation power, the radio frequency, the flow concentration or pressure, the temperature and the desired thickness of the grafted material. Preferably, the radiation power is about 10 watts to about 200 watts, depending upon the biocompatible material. For example, where the biocompatible material comprises silazane, hexamethyldisiloxane, PMMA, NVP or PAA, it is presently preferred that the radiation power is about 50 watts. Where the biocompatible layer material comprises HEMA (discussed below), it is presently preferred that the radiation power is about 10 watts to about 100 watts. In any event, except where desired, the reactor power used and the duration such power is used should be low and/or short enough so as to not induce thermal circulation and melt the substrate material. For example, where the substrate material comprises PMMA, the reaction conditions (i.e., power and duration) should not increase the temperature of the substrate material above about 40°-45° C. One skilled in the art may readily determine, in view of the plasma reaction variables described above, the desired plasma radiation power to be used in accordance with the present invention.

The plasma reaction is preferably conducted for a period of time of about 1 minute to about 60 minutes. More preferably, the plasma reaction is allowed to occur for a period of time of about 15 minutes to about 30 minutes. The flow concentration or vapor pressure of the plasma reactants in the reactor chamber should be low enough so that the particular monomer of the biocompatible material vaporizes when introduced into the reactor. Preferably, the vapor pressure is about 0.1 torr to about 0.6 torr. More preferably, the vapor pressure is about 0.4 torr.

The temperature in the plasma reaction should not be allowed to approach those temperatures which may damage the substrate material or the biocompatible material. High radiation power and any polymerization reaction (i.e., polymerization which may occur when the grafting reaction occurs; e.g., polymerization to polymethylmethacrylate) tend to increase the temperature of the plasma reaction. It is desirable, therefore, to maintain the temperature in the plasma reaction below the temperature at which the substrate material and/or the graft material will be damaged, typically below about 40°-50° C.

In another embodiment of the present invention where no biocompatible material is grafted to the substrate, a microscopically smooth surface is obtained by plasma treatment of the substrate surface sufficient to etch the substrate surface and raise the temperature at the substrate surface to a temperature just above the glass transition temperature (T_g) of the substrate material. While not wishing to be bound by any particular theory, the inventors believe that; plasma treatment to induce an increase in temperature causes a thermal annealing at the surface of the substrate whereby irregular surface features (such as surface peaks, etc.) relax, evening out such irregularities. Where temperatures above the glass transition temperature are desired, relatively higher radiation power is preferred. For example, to reach a surface temperature of about 105° C., which is the glass transition temperature of PMMA, radiation power of about 100 to about 120 watts is preferred. One skilled in the art may readily determine glass transition temperature by reference to publicly available materials characteristics tables and determine the temperature obtainable at a given wattage in a given reactor factoring in time, efficiency of the reaction chamber and the surface area of the substrate, for example. The radiation power used and the time the substrate is exposed to such radiation should be such to avoid thermal circulation of the substrate beneath the surface and melting of the substrate.

In view of this disclosure, one skilled in the art may readily determine the reactants, time, pressure and temperature conditions for a reaction using given materials without undue experimentation. For example, in one embodiment of the present invention, methyl methacrylate liquid is introduced into a plasma reactor chamber having a plasma-etched or treated body of PMMA where, because of the low pressure within the chamber, the methyl methacrylate vaporizes. The methyl methacrylate is exposed to about 50 to about 150 watts of radio frequency radiation at about 27.5° C. at a reactant or vapor pressure of about 0.4 to about 0.5 Torr.

Novel products having a permanently modified surface resulting from the method of the present invention include prostheses, such as an intraocular lens, for use in mammals having a permanently modified, biocompatible surface, which comprises a polymer lens body and a biocompatible, polymeric material grafted thereto, where the biocompatible, polymeric material comprises substantially the same material as the material forming the polymer lens body, such as PMMA.

In addition, novel products produced using the method of the present invention include prostheses for use in mammals comprising a polymeric material substrate having a permanently modified surface where the surface was modified by subjecting the substrate surface to radio frequency plasma sufficient to raise the temperature at the substrate surface to just above the glass transition temperature.

The invention will now be illustrated in further detail by reference to the following specific, non-limiting examples.

EXAMPLE I

An intraocular lens manufactured by CILCO from PMMA was abraded using 1 micron aluminum oxide particles to produce grooves on the surface of the lens of 1 micron depth. Macroscopically, the lens had a hazy appearance. The lens was cleaned in a 1% sodium dodecyl sulfate (SDS) solution and then thoroughly rinsed in deionized water to remove any contaminants that may be present from the manufacturing process or subsequent handling. The lens was positioned in a Branson 3000 Series radio frequency plasma reactor in a glass treatment fixture. The pressure inside the reactor was reduced to less than about 0.1 Torr for approximately 10 minutes. Argon gas (Ar) was then introduced at approximately 8 psi and the pressure inside the reactor was adjusted to 0.5 Torr for 10 minutes to purge the chamber with the argon gas. Radio frequency power was then turned on to 120 watts while maintaining chamber pressure at 0.5 Torr. Treatment with the argon gas plasma continued for approximately 60 minutes. After this time, radio frequency power was turned off and the chamber was purged to normal atmospheric pressure to open the chamber door. Macroscopically, the lens appeared clean and clear. Upon microscopic examination, some surface irregularities or memory of the initial grooves was apparent.

EXAMPLE II

An intraocular lens was treated using the procedures of Example I. After turning off the radio frequency power, the chamber was then pumped down to a pressure of 0.1 Torr for approximately 5 minutes to evacuate the chamber. Methylmethacrylate (MMA) monomer was then introduced into the reactor chamber at maximum flow rate (approximately 0.8 Torr) and radio frequency power was turned on to 70 watts for 30 minutes. After this time, MMA delivery was discontinued and the radio frequency power was shut down. The chamber was then purged to normal atmospheric pressure to open the chamber door. Macroscopically and microscopically, the lens was free of any surface irregularities, surpassing the surface quality of the original, commerical lens.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than the specification, as indicating the scope of the invention.

We claim:

1. A method of permanently modifying the surface of a polymeric substrate material to produce a microscopically smooth, biocompatible surface thereon, comprising covalently grafting a polymeric biocompatible material to the surface of the substrate material by radio frequency plasma induction, the biocompatible polymeric material comprising the same material as the polymeric substrate.

2. The method according to claim 1, wherein the grafting is induced in a radio frequency plasma reactor generating a frequency of about 1 MHz to about 40 MHz.

3. The method according to claim 2, wherein the frequency is about 13.56 MHz.

4. The method according to claim 2, wherein gas is present in the reactor, said gas being selected from the group consisting of noble gases.

5. The method according to claim 4, wherein the gas is argon.

6. The method according to claim 1, wherein the biocompatible polymeric material comprises polyacrylic acid, silicone, polypropylene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, polymethylmethacrylate or polymers of ethylenediamine, diethylenetriamine, allylamine or hydroxyethylmethacrylate.

7. A method of permanently modifying the surface of a substrate polymeric material, comprising subjecting the substrate surface to radio frequency plasma sufficient to raise the temperature at the substrate surface to just above the glass transition temperature of the substrate material for a time sufficient to produce a microscopically smooth, biocompatible surface on the substrate material.

8. The method according to claim 7, wherein the substrate material is selected from the group consisting of polyacrylic acid, silicone, polypropylene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, polymethylmethacrylate and polymers of ethylenediamine, diethyltriamine, allylamine or hydroxyethylmethacrylate.

9. The method according to claim 7, wherein the plasma is generated in a radio frequency plasma reactor generating a frequency of about 1 MHz to about 40 MHz.

10. The method according to claim 9, wherein gas is present in the reactor, said gas being selected from the group consisting of noble gases.

11. The method according to claim 10, wherein the radio frequency plasma reactor radiates at a power of about 100 watts to about 200 watts.

12. The method according to claim 7, further comprising covalently grafting a polymeric biocompatible material to the surface of the substrate material by radio frequency plasma induction.

13. A method of manufacturing a prosthesis comprising providing a polymeric prosthesis core and covalently grafting a polymeric biocompatible material to a surface of the core by radio frequency plasma induction, such that the prosthesis is provided with a microscopically smooth, biocompatible surface.

* * * * *

EXHIBIT D

US005326584A

United States Patent [19]

Kamel et al.

[11] Patent Number: 5,326,584

[45] Date of Patent: * Jul. 5, 1994

[54] BIOCOMPATIBLE, SURFACE MODIFIED MATERIALS AND METHOD OF MAKING THE SAME

[75] Inventors: Ihab Kamel, Philadelphia; David B. Soll, Rydall, both of Pa.

[73] Assignees: Drexel University; Ophthalmic Research Corporation, both of Philadelphia, Pa.

[*] Notice: The portion of the term of this patent subsequent to Jan. 14, 2009 has been disclaimed.

[21] Appl. No.: 977,984

[22] Filed: Nov. 18, 1992

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 820,169, Jan. 13, 1992, Pat. No. 5,260,093, which is a continuation-in-part of Ser. No. 342,270, Apr. 24, 1989, Pat. No. 5,080,924.

[51] Int. Cl.[5] B05D 3/06

[52] U.S. Cl. 427/491; 427/534; 427/307; 156/643

[58] Field of Search 427/534, 491, 307, 2; 156/643, 668

[56] References Cited

U.S. PATENT DOCUMENTS

2,999,056	9/1961	Tanner	522/118
3,228,741	1/1966	Becker	351/160 R
3,880,818	4/1975	Shen et al.	526/322
3,925,178	12/1975	Gesser et al.	204/165
3,944,709	3/1976	Levy	428/409
3,959,105	5/1976	Feneberg et al.	204/165
3,961,379	6/1976	Highgate	522/116
3,985,697	10/1976	Urbach	523/106
4,055,378	10/1977	Feneberg et al.	351/160
4,072,769	2/1978	Lidel	427/38
4,096,315	6/1978	Kubacki	428/412
4,099,859	7/1978	Merrill	351/160 H
4,122,942	10/1978	Wolfson	206/5.1
4,123,308	10/1978	Nowlin et al.	427/41
4,131,691	12/1978	Morley et al.	427/41
4,137,365	1/1979	Wydeven et al.	428/412
4,143,949	3/1979	Chen	427/41
4,189,364	2/1980	Aellon et al.	522/4
4,214,014	7/1980	Hofer et al.	427/40
4,240,163	12/1980	Galin	623/6

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

2119957	11/1983	United Kingdom	351/160 R

OTHER PUBLICATIONS

H. Yasuda, "Plasma for Modification of Polymers," *J. Macromol. Sci.-Chem.*, A10(3), pp. 383–420 (1976).

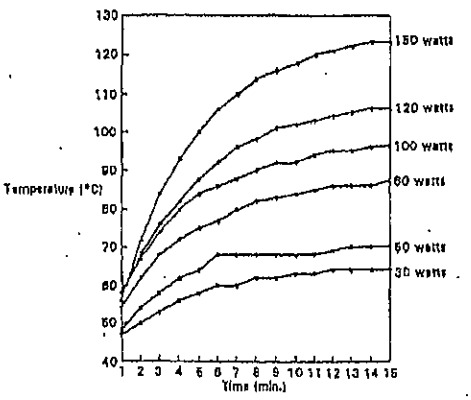
(List continued on next page.)

Primary Examiner—Shrive Beck
Assistant Examiner—Brian K. Talbot
Attorney, Agent, or Firm—Panitch Schwarze Jacobs & Nadel

[57] ABSTRACT

The present invention includes methods of permanently modifying the surface of a substrate material so as to develop a microscopically smooth, biocompatible surface thereon. A portion of the substrate surface is first removed, as by etching, in a radio frequency plasma reactor using inert argon gas. A biocompatible polymeric material may be covalently grafted to the surface of the substrate material by radio frequency plasma-induced grafting. The biocompatible polymeric material is preferably the same as the substrate material but may be different. Alternatively, after etching, the surface of a substrate material may be subjected to radio frequency plasma sufficient to raise the temperature at the substrate surface to just above the glass transition temperature (T_g) of the substrate material for a time sufficient to produce a microscopically smooth, biocompatible surface on the substrate material. Further, the present invention includes a prosthesis used in mammals, including an intraocular lens, having a polymeric material core and a biocompatible polymeric material covalently grafted to the polymer core by radio frequency plasma treatment.

19 Claims, 1 Drawing Sheet



U.S. PATENT DOCUMENTS

4,277,595	7/1981	Deichert et al.	528/26
4,311,828	1/1982	Imada et al.	528/483
4,312,575	1/1982	Peyman et al.	351/160 H
4,328,257	5/1982	Muehlberger et al.	427/34
4,344,981	8/1982	Imada et al.	427/40
4,405,773	9/1983	Loshaek et al.	526/318.42
4,409,258	10/1983	Feurer et al.	427/38
4,430,458	2/1984	Tighe et al.	523/108
4,463,148	7/1984	Hofer et al.	526/264
4,478,873	10/1984	Masso et al.	427/40
4,560,458	12/1985	Ueno et al.	204/165
4,632,842	12/1986	Karwoski et al.	427/2
4,656,083	4/1987	Hoffman et al.	427/41
4,718,907	1/1988	Karwoski et al.	623/12
4,720,512	1/1988	Hu et al.	523/112
4,731,080	3/1988	Galin	623/6
4,865,870	9/1989	Hu et al.	427/2
4,885,077	12/1989	Karakelle et al.	427/41
4,919,659	4/1990	Horbett et al.	427/2
4,927,676	5/1990	Williams et al.	427/2
5,002,582	3/1991	Guire et al.	623/66
5,080,924	1/1992	Kamel et al.	427/412.3
5,091,240	2/1992	Ratner et al.	427/2
5,093,152	3/1992	Bonet et al.	427/307

OTHER PUBLICATIONS

Knight et al., "Surface Modification of Intraocular Lenses to Reduce Corneal Endothelial Damage," *AM Intra-Ocular Implant Soc. J*-vol. V, pp. 123-130, Apr. 1979.

Gazard et al., "Lithographic Technique Using Radiation-Induced Grafting of Acrylic Acid into Poly(-Methyl Methacrylate)Films," *Polymer Engineering and Science*, vol. 20, No. 16, pp. 1069-1072 (1980).

K. L. Mittal, "Interfacial Chemistry and Adhesion: Recent Developments and Prospects," *Pure & Appl. Chem.*, vol. 52, pp. 1295-1305 (1980).

Akovali et al., "Polymerization of Hexamethyldisiloxane by Plasma on Activated Charcoal: Investigation of Parameters," *Journal of Applied Polymer Science*, vol. 29, pp. 2617-2625 (1984).

Liu et al., "Polymethyl Methacrylate Resist Sensitivity Enhancement in X-Ray Lithography by In Situ Polymerization," *Appl. Phys. Lett.*, 44(10), pp. 973-975, May 15, 1984.

Keates et al., "Coated Intraocular Lenses," *Ophthalmic Surgery*, vol. 18, No. 9, pp. 693-697 (1987).

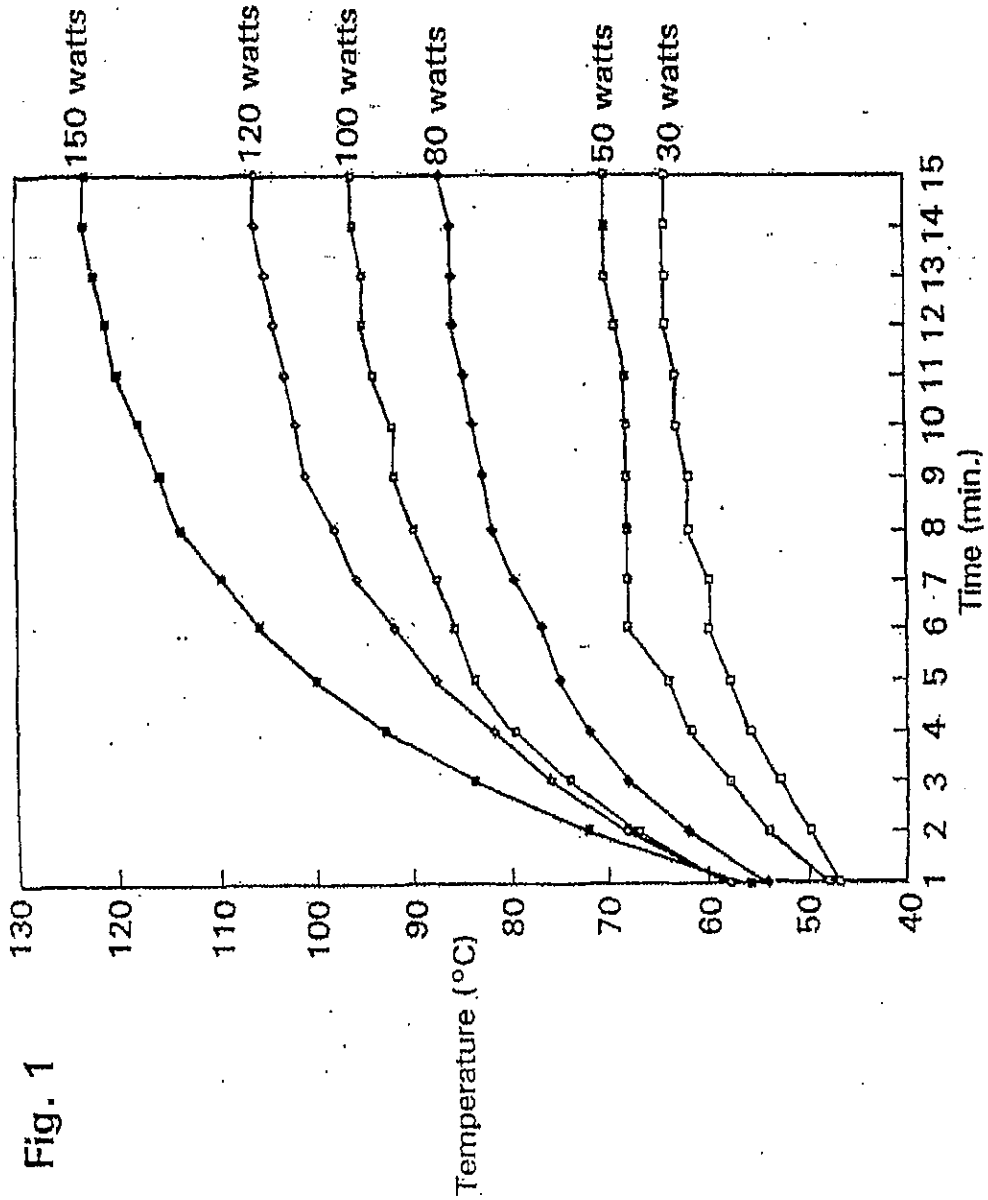

150 watts
120 watts
100 watts
80 watts
50 watts
30 watts
Temperature (°C)
130
120
110
100
90
80
70
60
50
40
Time (min.)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Fig. 1

BIOCOMPATIBLE, SURFACE MODIFIED MATERIALS AND METHOD OF MAKING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation-in-part application of our copending U.S. patent application Ser. No. 07/820,169, now U.S. Pat. No. 5,260,093 filed Jan. 13, 1992, which is a continuation-in part of application Ser. No. 07/342,270, filed Apr. 24, 1989 now U.S. Pat. No. 5,080,924.

FIELD OF THE INVENTION

The present invention relates to methods of permanently modifying the surface of materials by plasma-induced and, where desired, post-plasma reactions to produce biocompatible, surface modified materials. In addition, the present invention relates to biocompatible, surface modified prostheses and, in particular, to a biocompatible, surface modified intraocular lens used in mammals.

BACKGROUND OF THE INVENTION

Prosthetic devices or prostheses are commonly used in medical procedures to replace or augment defective organs in mammals and humans. Such prostheses are numerous and diverse in structure and application. Examples of prostheses include artificial joints, valve replacements, artificial skin, vascular grafts, shunts, plates and contact and intraocular lenses. Typical prosthetic materials include metals, ceramics, silicone rubbers, polyesters, polyurethanes and/or polysulfones. Synthetic polymers, such as polymethylmethacrylate (PMMA), silicone elastomers and polymers of hydroxyethylmethacrylate (HEMA), are preferred polymers for prosthetic use in general and contact lenses and intraocular lenses in particular.

PMMA has several beneficial characteristics for prosthetic use, including excellent light transmission capability, good optical clarity, resistance to fluid diffusion and in vivo deterioration, ease in processing (injection molding or machining, for example) and ease in implantation.

A problem with typical prior prostheses, such as lens prostheses, is that they are manufactured by machining and also some by injection molding. In the former, the machining process typically leaves circular lathe marks or grooves visible at even relatively low magnification. These machining marks render the lens unusable until the lens surface is smoothed, typically by a mechanical polishing process. However, conventional polishing processes generally take several days to complete, have failure rates in excess of 30% and fail to produce a microscopically smooth surface. The surfaces of injection molded lenses do not show machine lathe marks. However, their surfaces are also not microscopically smooth and reflect the surface finish of the mold.

Also, typical prosthetic devices comprise natural and/or synthetic materials which are highly irregular on the cellular level. These rough prostheses, especially those which are implanted, can cause tissue irritation, cell proliferation, edema and scarring. For example, posterior lens capsule opacification is a prevalent problem among those patients who have received intraocular lens implants comprising conventionally polished PMMA and other similar materials. Pseudophakic precipitates on the surfaces of an intraocular lens can be indicative of microscopic surface irregularities.

It is desirable to modify the surface properties of such abrasive materials without changing the beneficial characteristics thereof by developing a microscopically smooth surface to discourage tissue adhesion and inhibit unwanted cellular growth. Prostheses which do not promote tissue adhesion, which inhibit cellular growth, and which are not otherwise toxic to living systems may be considered "biocompatible." The biocompatible modified surface should be resistant to deterioration over time and should have no adverse effects on contacting tissues and cells.

Those skilled in the art have long recognized the need for biocompatible, surface modified materials for use in prosthetic devices and other materials. For example, U.S. Pat. No. 3,961,379 discloses a bioimplantable device manufactured from a cross-linked, swollen, hydrophilic polymer. These modified polymers must be solid and must be swellable by fluid swelling substances. Once swollen, the solid polymer is polymerized with a modifying substance by, for example, high energy particle radiation.

U.S. Pat. No. 4,189,364 discloses hydrophilic polymers formed in situ by irradiating a mixture of hydroxyalkyl methacrylate and a cross-linking agent. This patent discloses a process for forming hydrophilic polymer articles or hydrophilic polymer coatings on other substrates, such as glass or plastic, by polymerizing a hydrophilic monomer system by high energy particulate irradiation, such as accelerated electrons or nuclear particles including neutrons, protons, alpha, beta and/or gamma particles.

Radiation-induced grafting of acrylic acid onto other polymer films is disclosed by Gazard, M. et al., "Lithographic Technique Using Radiation-Induced Grafting of Acrylic Acid Into Poly(Methyl Methacrylate) Films," *Polymer Engineering and Science*, 20:16 (1980). Gazard et al. disclose that, under ionizing radiation, polymer properties, such as solubility, may be modified. Ionizing radiation of polymers leads to the formation of free radicals and other intermediates, which may be used to initiate the grafting of a monomer to produce a grafted copolymer with properties different from those of the initial polymer. For example, a grafted copolymer of irradiated PMMA and acrylic acid is insoluble in solvents of PMMA.

U.S. Pat. No. 2,999,056 also discloses that an unsaturated organic acid may be attached to a shaped polymeric structure by ionizing radiation.

Other methods of altering the surface of polymeric objects include exposing the surface of a polymeric article to low temperature plasma or an electrically charged gaseous atmosphere, followed by contacting the surface of the polymeric article with a surface modifying compound as described, for example, in U.S. Pat. No. 4,344,981. This two-step method is generally called plasma-induced coating. Plasma induction has been described generally in U.S. Pat. No. 4,328,257, Yasuda, "Plasma for Modification of Polymers," *J. Macromol. Sci. C. Chem.*, 10(3):383 (1978), Mittal, "Interfacial Chemistry and Adhesion: Recent Developments and Prospects," *Pure & Appl. Chem.*, 52: 1295 (1980), Akovali, G. and Hasirci, N., "Polymerization of Hexamethyldisiloxane by Plasma on Activated Charcoal: Investigation of Parameters," *J. Appl. Polymer Sci.*, 29:2617 (1984) and Liu, W. T. et al., "Polymethyl Meth-

acrylate Resist Sensitivity Enhancement in X-Ray Lithography by In Situ Polymerization," *Appl. Phys. Lett.*, 44:973 (1984), for example.

Ionized vapor or a plasma discharge is typically created in a vacuum chamber in which the object to be modified is placed. The plasma discharge conditions the surface of the object by creating free radicals and/or ions. It is known, for example, that exposing the surface of an object to a plasma discharge, such as an oxygen plasma, enhances the wettability or hydrophilicity of such a surface. However, such treatment is only temporary. U.S. Pat. Nos. 3,925,178; 3,944,709; 4,072,769; 4,096,315; 4,122,942; 4,123,308; 4,131,691; 4,137,365; 4,214,014 and 4,478,873 disclose examples of polymers whose surface characteristics have been modified by a plasma discharge.

Plasma discharge treatment may also be used to prepare an object for the attachment or grafting of a compound or material to the plasma discharge treated object. For example, a plasma discharge step may be used to condition the surface for grafting by creating free radicals to which a compound or material may be grafted. Such compounds or materials are generally called surface modifiers. Knight, P.M. et al., in "Surface Modification of Intraocular Lenses to Reduce Corneal Endothelial Damage, "*Am. Intra-ocular Implants Soc. J.*, 5:123 (1979) disclose one example of a polymer object having a surface modifier attached thereto using gamma irradiation and radio frequency (RF) gas plasma treatment to generate free radicals on the surface of a PMMA intraocular lens followed by polymerizing hydrophilic monomers, in particular, HEMA and vinyl pyrrolidone, as a coating on the surface of the lens. While the coated surfaces exhibited enhanced hydrophilicity, the coated surfaces were not stable when sterilized by boiling. Surface modification by gamma radiation followed by polymerization on the surface, on the other hand, remained intact through several hours of boiling. However, such coated PMMA surfaces were damaging to rabbit endothelial cells and surfaces coated with dissolvable coatings, such as polyvinyl acetate, were preferred.

Another example of a surface treated polymer is disclosed in U.S. Pat. No. 4,312,575. This patent discloses a soft, highly oxygen permeable, hydrophobic polymeric lens which has a surface coating of an ultra-thin, optically clear, permeable barrier. The coating is the reaction product resulting from a glow discharge polymerization process conducted in a hydrocarbon or halogenated hydrocarbon gaseous atmosphere. While the plasma discharge process, itself, results in a hydrophilic surface, this patent discloses that subsequent exposure to a glow discharge atmosphere of oxygen or ambient oxygen yields a still more hydrophilic surface.

U.S. Pat. No. 4,409,258 discloses a method for rendering contact lenses hydrophilic by bombarding the lens of PMMA or silicone, for example, with a positive ion beam generated by a plasma discharge, such as an oxygen plasma. The lens is thereafter hydrated, preferably at an elevated temperature.

Examples of surface treated polymeric lenses for use in humans are included in U.S. Pat. No. 3,880,818. This patent discloses a soft contact lens that is flexible and physiologically compatible. The lens is made by manufacturing a hard, inflexible prepolymer, such as a hard acrylic acid-type polymer, and reacting the inflexible prepolymer with an alcohol to esterify pendant carboxyl groups with alkyl groups, hydroxy alkyl groups or alkoxyalkyl groups, containing no more than eleven carbon atoms.

U.S. Pat. No. 4,143,949 discloses a discharge polymerization and coating process for making a hydrophilic contact lens from an oxygen permeable, hydrophobic polymer. The hydrophobic lens is placed in a glow discharge apparatus containing an atmosphere comprising a polymerizable organic monomer, such as hydroxyalkyl acrylate or methacrylate, glycidyl methacrylate, propylene oxide or N-vinyl-2-pyrrolidone. The glow discharge is used to polymerize the monomer onto the surface of the contact lens.

Other examples of surface treated polymeric objects include U.S. Pat. Nos. 3,228,741; 3,959,105; 3,985,697; 4,055,378; 4,277,595; 4,405,773; 4,430,458; 4,463,148; and 4,731,080. U.S. Pat. No. 4,731,080, for example, discloses a coated intraocular lens having a hydrophobic cross-linked vinyl-containing silicone polymer placed on the lens surface in solution.

It would be desirable to have a biocompatible, surface modified material and a method for producing the same, wherein the surface of the substrate material is cleaned, and active species, such as ions and free radicals, are produced on the surface by a plasma treatment to enhance subsequent grafting of a polymeric biocompatible material to the substrate surface to provide a substantially permanent, smooth surface on a cellular level. A method for grafting a polymeric biocompatible material to the surface of a substrate is disclosed in our U.S. Patent No. 5,080,924 and U.S. Pat. No. 5,260,093 the disclosures of which are incorporated herein by reference. By pretreating the surface of the substrate material, the smoothness of the substrate and the grafted surface may be improved.

BRIEF DESCRIPTION OF THE INVENTION

According to the present invention, a method is provided for permanently modifying a surface of a polymeric substrate material so that the substrate material develops a microscopically smooth, biocompatible surface. The method comprises removing at least a portion of the surface of the polymeric substrate material and covalently grafting a biocompatible polymeric material to the surface of the substrate material by radio frequency plasma treatment. The biocompatible polymeric material comprises substantially the same material as the polymeric substrate.

Another aspect of the present invention is another method for permanently modifying a surface of a substrate polymeric material. The method comprises the steps of removing at least a portion of the surface of the polymeric substrate material by subjecting the substrate surface to inert gas radio frequency plasma sufficient to raise the temperature at the substrate surface to just above the glass transition temperature of the substrate material for a time sufficient to produce surface relaxation and a resulting microscopically smooth, biocompatible surface on the substrate material.

Yet another aspect of the present invention is a prostheses used in mammals which has a permanently modified microscopically smooth, biocompatible surface. The prostheses comprises a polymeric material core having an etched surface and a biocompatible material grafted to the surface of a polymer core by radio frequency plasma treatment. The biocompatible polymeric material comprises substantially the same material as the core.

Another aspect of the present invention is an intraocular lens having a permanently modified, smooth, biocompatible surface. The lens comprises a polymeric material lens body having an etched surface and a biocompatible polymeric material. The biocompatible polymeric material is grafted to the surface of the lens body and comprises substantially the same material as the body.

A further aspect of the present invention is a method of manufacturing a prostheses to provide the prostheses with a microscopically smooth, biocompatible surface without the use of mechanical polishing. The method comprises the steps of etching a surface of a polymeric prostheses core and covalently grafting a polymeric biocompatible material to the surface of the core by radio frequency plasma treatment.

BRIEF DESCRIPTION OF THE DRAWING

The foregoing summary, as well as the following detailed description of the preferred embodiments, will be better understood when read in conjunction with the appended drawing. For the purpose of illustrating the invention, there is shown in the drawing one embodiment, it being understood, however, that the invention is not limited to the specific method and instrumentality disclosed. In the drawing:

FIG. 1 is a graph of surface temperature of PMMA substrates as a function of time at various radio frequency power levels which shows the thermal annealing effect of argon plasma where the temperature of the substrate surface increases with plasma power and can be made to exceed the glass transition temperature, according to one embodiment of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Although the methods of modifying the surface of a polymeric substrate material according to the present invention apply generally to many different materials, the methods are described and examples are given below for polymeric intraocular lenses as prostheses which may be used in mammals. It will be understood by one of ordinary skill in the art that the methods of the present invention may be used to prepare permanently modified surfaces of other substrate materials, such as those prosthestic materials identified above. Moreover, it will be apparent to an ordinary skilled artisan that the methods of the present invention readily lend themselves to the preparation of materials having modified or enhanced surface characteristics having other uses.

Examples of polymeric substrate materials which are useful in the present invention include polymers, such as silicone elastomers, polypropylene, polyesters, such as polyethylene terephthalate, polytetrafluoroethylene, polyurethane, ethylenediamine, PMMA, ethylenediamine, polyacrylic acid, and polymers of HEMA, ethylenediamine, diethylenetriamine, allylamine hexamethyldisiloxane, silazane and N-vinyl pyrrolidone.

Generally, the substrate material used in accordance with the present invention is chosen dependent upon its intended use. For example, PMMA, HEMA and silicone are useful for making prosthetic devices intended for implantation or other applications in mammals. However, in view of the present specification, one of ordinary skill in the art will appreciate that any biocompatible organic polymer may be used as a substrate material, as well as certain ceramics. Where an optically clear polymer for use in prosthetic devices for mammals is desired as the substrate material, it is presently preferred that the polymer comprise PMMA or a silicone elastomer.

According to the method of the present invention, at least a portion of the surface of the polymeric substrate material is removed to clean the substrate and produce active species on the polymer surface, such as ions and free radicals, which can be used for inducing a grafted reaction. Preferably, the removal of the portion of the surface material is accomplished by inert gas etching. The etching may be induced in a radio frequency (RF) plasma reactor, such as are well known to those of ordinary skill in the art. The Branson Model 3003-1813 is one example of a suitable radio frequency gas plasma reactor which may be used to etch the surface of the polymeric substrate material. One skilled in the art will appreciate, however, that other plasma reactors and apparatus may be used in accordance with the present invention.

Generally, the rate of material removal is influenced by the frequency or power of the gas plasma, the treatment time, the gas used in the plasma reactor, the gas pressure/concentration and the type of bond present on the treated substrate material surface, depending on the particular substrate material. For the Branson Model 3003-1813 radio frequency plasma reactor, frequency is kept at 13.56 MHz, which is suitable for etching.

Preferably, the etching process includes injecting a noble or ambient gas into the reactor to create ions which bombard the substrate creating active sites on the substrate surface. Nitrogen and ammonia gases are also believed to be useful in the radio frequency gas plasma reaction when nitrogenous compounds are desired. Preferably, the noble gas is argon, which creates active sites on the substrate surface but does not produce new chemical groups when applied to the substrate surface in a RF gas plasma reactor. Where no biocompatible material is to be grafted to the substrate surface (discussed below) or where the presence of new chemical groups on the substrate surface is not desired, it is presently preferred to use a noble gas, such as argon, as the RF gas in the plasma reactor. Oxygen, on the other hand, for example, tends to produce peroxides in such plasma-induced grafting reactions and is, therefore, generally less stable chemically. One of ordinary skill in the art will be readily able to determine in view of this disclosure suitable gases which may be used in the plasma reaction in accordance with the present invention.

The substrate surface to be etched is first cleaned with a mild soap solution, i.e., a 1% sodium decyl sulphate solution, and rinsed in deionized water to remove any contaminants that may be present from the manufacturing processes and subsequent handling. The lens is positioned in the radio frequency plasma reactor on a glass or other suitable fixture. The pressure in the reactor is reduced to less than about 0.05 to about 0.1 torr for about 5 to about 10 minutes. Argon gas is introduced into the chamber at a pressure of about 8 to about 10 psi and the pressure within the reaction chamber is adjusted to about 0.3 to about 0.5 torr for about 5 to about 10 minutes to purge the chamber with the argon gas. Radio frequency power was applied at about 50 to about 200 watts for about 30 to about 60 minutes while maintaining the pressure level at about 0.3 to about 0.5 torr. The RF power supply is discontinued and the chamber is maintained at a pressure of about 0.3 to about 0.5 torr for about 5 to about 10 minutes. One of ordinary skill in

the art would understand that the pressure levels, power levels and times may vary based upon such variables as the substrate material, different reactors, and the choice of ambient gas.

In one embodiment of the present method, after etching of the substrate surface, the substrate surface may be subjected to radio frequency plasma sufficient to raise the temperature at the substrate surface to just above the glass transition temperature of the substrate material for a time sufficient to produce a microscopically smooth, biocompatible surface on the substrate material.

While not wishing to be bound by any particular theory, the inventors believe that plasma treatment to induce an increase in temperature causes a thermal annealing at the surface of the substrate whereby irregular surface features (such as surface peaks, etc.) relax, evening out such irregularities.

FIG. 1 is a graph of substrate surface temperature of PMMA substrates as a function of time at several power levels ranging from 30 to 150 watts. As shown in FIG. 1, the temperature of the substrate surface increases during plasma treatment. For example, at 150 watts of power, the temperature of the substrate climbs about 60° C. after 10 minutes of plasma treatment.

Where temperatures above the glass transition temperature are desired, relatively higher radiation power is preferred. For example, to reach a surface temperature of about 105° C., which is the glass transition temperature of PMMA, radiation power of about 120 to about 150 watts is preferred. One skilled in the art may readily determine glass transition temperature by reference to publicly available material characteristic tables and experimentally determine the temperature obtainable at a given wattage in a given reactor. Other temperatures can then be calculated by factoring in time, efficiency of the reaction chamber, the surface area of the substrate and reactor power, for example. The radiation power used and the time the substrate is exposed to such radiation should be such to avoid subsurface thermal circulation and melting of the substrate.

In an alternative embodiment, the method includes a step of covalently grafting a polymeric biocompatible material to the surface of the substrate material by radio frequency plasma treatment. Preferably, the biocompatible polymeric material is introduced in the monomer form and is selected from ethylenediamine, hexamethyldisiloxane, acrylic acid, diethylenetriamine, allylamine, hydroxyethylmethacrylate, methylmethacrylate and combinations thereof, for example.

The resulting biocompatible polymeric material is preferably grafted to the substrate material in a relatively uniform thickness and texture along the surface of the substrate material. In addition, especially where it is desired to use the substrate material as a prosthetic lens, it is preferred that the biocompatible polymeric material is present on the surface of the substrate material in a relatively uniform, small thickness to prevent interference with the optical clarity of the lens. More preferably, the biocompatible polymeric material is present in few molecular layers. In one embodiment of the present invention, for example, a surface modified substrate comprises a biocompatible polymeric material grafted to the surface of a substrate material with a biocompatible polymeric material thickness of about 100 Å.

Grafting of the biocompatible polymeric material according to the present invention is conducted using radio frequency plasma-induced grafting. Other methods of grafting, such as electron beam or ultra-violet (UV) radiation, are not suitable where it is desired to modify only the surface of the substrate material. For example, where a prosthetic lens, such as a contact lens or intraocular lens, is desired to be modified, modification should be confined to the surface of the lens to avoid affecting the optical properties of the lens. Radio frequency plasma-induced grafting according to the present invention avoids structural modification below the outer-most surface layer, and generally results in more desirable optical properties.

Such gas plasma-induced grafting may be conducted in a radio frequency gas plasma reactor such as that discussed above capable of generating a frequency of about 1 MHz to about 40 MHz. The frequency generated by a typical commercial gas plasma reactor is 13.56 MHz, although one skilled in the art will recognize that higher and lower frequencies may be used to graft the biocompatible polymeric material to the surface of the substrate material in a radio frequency gas plasma reactor, depending on the substrate material and biocompatible polymeric material used, the relative ease or difficulty in preparing the surface of the substrate material for grafting, the relative ease or difficulty of vaporizing or polymerizing the biocompatible material, among other factors.

The length of time the biocompatible material in an induced plasma state should be allowed to react with the substrate material depends upon several factors, including the plasma or radiation power, the radio frequency, the flow concentration or pressure, the temperature and the desired thickness of the grafted material. Preferably, the radiation power is about 10 watts to about 200 watts, depending upon the biocompatible material. For example, where the biocompatible material comprises silazane, hexamethyldisiloxane, MMA, NVP or AA, it is presently preferred that the radiation power is about 50 watts. Where the biocompatible layer material comprises HEMA (discussed below), it is presently preferred that the radiation power is about 10 watts to about 200 watts.

In any event, except where desired, the reactor power used and the duration during which such power is used should be low and/or short enough so as to not induce thermal circulation and melt the substrate surface. For example, where the substrate material comprises PMMA, the reaction conditions (i.e., power and duration) should not increase the temperature of the substrate material above about 40°–60° C. One skilled in the art may readily determine, in view of the plasma reaction variables described above, the desired plasma radiation power to be used in accordance with the present invention.

The temperature in the plasma reaction should not be allowed to approach those temperatures which may structurally damage the substrate material or the biocompatible material. High radiation power and any polymerization reaction (i.e., polymerization which may occur when the grafting reaction occurs; e.g.: polymerization to polymethylmethacrylate) tend to increase the temperature of the plasma reaction zone. It is desirable, therefore, to maintain the temperature in the plasma reaction below the temperature at which the substrate material and/or the graft material will be damaged, typically below about 60°–80° C.

The flow concentration or vapor pressure of the plasma reactants in the reactor chamber should be low enough so that the particular monomer of the biocom-

patible material vaporizes when introduced into the reactor. Preferably, the vapor pressure is about 0.1 torr to about 0.6 torr. More preferably, the vapor pressure is about 0.4 torr.

The plasma reaction is preferably conducted for a period of time of about 1 minute to about 60 minutes. More preferably, the plasma reaction is allowed to occur for a period of time of about 15 minutes to about 30 minutes. The flow of biocompatible material into the reactor chamber may be continued for a period of time after the RF power supply to the reactor is terminated. The continued supply of biocompatible material is believed to quench long-lived radicals that could be present on some substrates.

In view of this disclosure, one skilled in the art may readily determine the reactants, time, pressure and temperature conditions for a reaction using given materials without undue experimentation. For example, in one embodiment of the present invention, methyl methacrylate liquid is introduced into a plasma reactor chamber having a plasma-etched or treated body of PMMA where, because of the low pressure within the chamber, the methyl methacrylate vaporizes. The methyl methacrylate is exposed to about 50 to about 150 watts of radio frequency radiation at about 20°-30° C. where its vapor pressure is about 0.4 to about 0.5 torr.

Where it is desired to have no change in the substrate surface chemistry, the biocompatible polymeric material is substantially the same as the material forming the substrate. Once the substrate material surface has been modified by covalently grafting the biocompatible material to the surface of the substrate material, the modified surface should have properties which are relatively nontoxic and nonirritating to living tissues. In addition, the modified surface should not adversely affect the desired properties of the remainder of the substrate material, such as structural integrity and optical clarity, among others. In addition, the modified surface should be microscopically smooth. As used herein, the term "microscopically smooth" shall mean that the surface of the modified substrate should be featureless upon examination at an enlargement of about 3,000 to about 10,000×, e.g. by SEM microscopy. In addition, where desired, and depending on the properties of the biocompatible polymeric material, the modified surface should show absence of crystallinity, cross-linked and thermally stable. The water contact angle should remain substantially unchanged after grafting of the biocompatible material to the substrate surface.

Where the substrate material is intended for use in or as a prosthetic device, such as an intraocular lens, the surface modification of the present invention should not adversely affect the transparency or ocular acuity of the substrate material. Further, the biocompatible material to be grafted to the substrate surface preferably comprises a material that is relatively easy to polymerize in a gas plasma environment. Such materials include unsaturated compounds or those compounds containing nitrogen, silicone or halogen. Materials that are relatively difficult to polymerize in a gas plasma environment include polymers, cyclic compounds, compounds with a high molecular weight, natural polymers such as proteins, and those compounds with extremely high vapor pressures.

Novel products having a permanently modified surface resulting from the method of the present invention include prostheses, such as an intraocular lens, for use in mammals having a permanently modified, biocompatible surface, which comprises a polymer lens body and a biocompatible, polymeric material grafted thereto, where the biocompatible, polymeric material comprises substantially the same material as the material forming the polymer lens body, such as PMMA.

In addition, novel products produced using the method of the present invention include prostheses for use in mammals comprising a polymeric material substrate having a permanently modified surface where the surface was modified by subjecting the substrate surface to radio frequency plasma sufficient to raise the temperature at the substrate surface to just above the glass transition temperature.

The invention will now be illustrated in further detail by reference to the following specific, non-limiting examples.

EXAMPLE I

An intraocular lens manufactured by Alcon/CILCO from PMMA was abraded using 1 micron aluminum oxide particles to produce grooves on the surface of the lens of 1 micron depth. Macroscopically, the lens had a hazy appearance. The lens was cleaned in a 1% sodium dodecyl sulfate (SDS) solution and then thoroughly rinsed in deionized water to remove any contaminants that may be present from the manufacturing process or subsequent handling. The lens was positioned in a Branson 3000 Series radio frequency plasma reactor in a glass treatment fixture. The pressure inside the reactor was reduced to less than about 0.1 torr for approximately 10 minutes. Argon gas (Ar) was then introduced at approximately 8 psi and the pressure inside the reactor was adjusted to 0.5 torr for 10 minutes to purge the chamber with the argon gas. Radio frequency power was then turned on to 120 watts while maintaining chamber pressure at 0.5 torr. Treatment with the argon gas plasma continued for approximately 60 minutes. After this time, radio frequency power was turned off and the chamber was purged to normal atmospheric pressure to open the chamber door. Macroscopically, the lens appeared clean and clear. Upon microscopic examination, some surface irregularities or memory of the initial grooves was apparent.

EXAMPLE II

An intraocular lens was treated using the procedures of Example I. After turning off the radio frequency power, the chamber was then pumped down to a pressure of 0.1 torr for approximately 5 minutes to evacuate the chamber. Methylmethacrylate (MMA) monomer was then introduced into the reactor chamber at maximum flow rate (approximately 0.8 torr) and radio frequency power was turned on to 70 watts for 30 minutes. After this time, MMA delivery was discontinued and the radio frequency power was shut down. The chamber was then purged to normal atmospheric pressure to open the chamber door. Macroscopically and microscopically, the lens was free of any surface irregularities, surpassing the surface quality of the original, commercial lens.

EXAMPLE III

A PMMA square sample manufactured by ICI Americas, Inc. of Wilmington, Del. had a contact angle of 79°. After abrading the sample using aluminum oxide particles having an average diameter of 1 micron to form 1 micron deep grooves on the sample surface, the contact angle was reduced to 77°. The sample was

cleaned with a 1% sodium decyl sulphate solution and rinsed with deionized water. The surface of the sample was etched using a Branson 3003-1813 RF plasma reactor by reducing the pressure in the reactor to less than about 0.1 torr for about 10 minutes and then purging the reactor chamber with argon gas at a pressure of 8 psi and reducing the pressure to about 0.5 torr for about 10 minutes. RF power was applied at about 100 watts for about 30 minutes while the argon pressure level was maintained at about 0.5 torr. The power supply was discontinued and the chamber evacuated to about 0.1 torr for about 5 minutes.

Methylmethacrylate (MMA) monomer was introduced into the reactor to maintain the chamber pressure at about 0.8 torr and the RF power was turned on to 50 watts. After 60 minutes, the MMA delivery and RF power supply were discontinued. The chamber was purged to normal atmospheric pressure. The contact angle of the sample after plasma treatment was 79°, which is equal to the contact angle measured prior to treatment. Therefore, the chemical nature of the surface of the sample was unchanged by grafting the MMA monomer thereto. For purposes of comparison, an untreated Coopervision TM PMMA intraocular lens has a measured contact angle of 74°.

TABLE I

Treatment	Contact Angle
ICI-PMMA sample without plasma treatment	79°
After abrasion	77°
After plasma treatment	79°
Coopervision-PMMA lens without plasma treatment	74°

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than the specification, as indicating the scope of the invention.

We claim:

1. A method of permanently modifying a surface of a polymeric substrate material to produce a microscopically smooth, biocompatible surface thereon, comprising the steps of:

removing at least a portion of the surface of the polymeric substrate material; and

covalently grafting a polymeric biocompatible material to the polymeric surface of the substrate material by radio frequency plasma treatment, the biocompatible polymeric material comprising substantially the same material as the polymeric substrate.

2. The method according to claim 1, wherein the polymeric substrate material is selected from the group consisting of polyacrylic acid, silicone elastomer, polypropylene, polyester, polyethylene terephthalate, polytetrafluoroethylene, polyurethane and polymethylmethacrylate.

3. The method according to claim 1, wherein the portion of the surface of the polymeric substrate material is removed by etching.

4. The method according to claim 3, wherein the etching is induced in a radio frequency plasma reactor.

5. The method according to claim 3, wherein the etching is induced in a radio frequency plasma reactor at a frequency of about 13.56 MHz.

6. The method according to claim 4, wherein the etching includes injecting a noble gas into the reactor.

7. The method according to claim 6, wherein the noble gas is argon.

8. The method according to claim 1, wherein the grafting is induced in a radio frequency plasma reactor generating a frequency of about 1 MHz to about 40 MHz.

9. The method according to claim 1, wherein the biocompatible polymeric material grafted to the substrate is selected from the group consisting of polymers of ethylenediamine, hexamethyldisiloxane, acrylic acid, diethylenetriamine, allylamine, hydroxyethylmethacrylate and methylmethacrylate.

10. A method of permanently modifying a surface of a polymeric substrate material, comprising the steps of:

removing at least a portion of the surface of the polymeric substrate material; and

subjecting the substrate surface to radio frequency plasma sufficient to raise the temperature at the substrate surface to just above the glass transition temperature of the substrate material surface for a time sufficient to produce a microscopically smooth, biocompatible surface on the substrate material.

11. The method according to claim 10, wherein the polymeric substrate material is selected from the group consisting of polyacrylic acid, silicone elastomer, polypropylene, polyester, polyethylene terephthalate, polytetrafluoroethylene, polyurethane and polymethylmethacrylate.

12. The method according to claim 10, wherein the portion of the surface of the polymeric substrate material is removed by etching.

13. The method according to claim 12, wherein the etching is induced in a radio frequency plasma reactor at a frequency of about 13.56 MHz.

14. The method according to claim 13, wherein the etching includes injecting a noble gas into the reactor.

15. The method according to claim 14, wherein the noble gas is argon.

16. The method according to claim 15, wherein the radio frequency plasma reactor operates at a power of about 100 watts to about 200 watts.

17. The method according to claim 10, further comprising covalently grafting a polymeric biocompatible material to the surface of the polymeric substrate material by radio frequency plasma treatment.

18. The method according to claim 17, wherein the grafting is induced in a radio frequency plasma reactor generating a frequency of about 1 MHz to about 40 MHz.

19. A method of manufacturing a prosthesis comprising the steps of:

etching a surface of a polymeric presthesis core; and

covalently grafting a polymeric biocompatible material to a surface of the core by radio frequency plasma treatment, whereby the prosthesis is provided with a microscopically smooth, biocompatible surface.

* * * * *

EXHIBIT E

US005578079A

United States Patent [19]

Kamel et al.

[11] Patent Number: 5,578,079

[45] Date of Patent: Nov. 26, 1996

[54] BIOCOMPATIBLE, SURFACE MODIFIED MATERIALS

[75] Inventors: Ihab Kamel, Drexel Hill; David B. Soll, Rydal, both of Pa.

[73] Assignees: Drexel University; Ophthalmic Research Corporation, both of Philadelphia, Pa.

[21] Appl. No.: 48,036

[22] Filed: Apr. 14, 1993

Related U.S. Application Data

[60] Division of Ser. No. 820,169, Jan. 13, 1992, Pat. No. 5,260,093, which is a continuation-in-part of Ser. No. 342,270, Apr. 24, 1989, Pat. No. 5,080,924.

[51] Int. Cl.[6] A61F 2/16

[52] U.S. Cl. ..... 623/6; 623/11; 623/66; 427/2.24; 427/2.25; 351/160 R

[58] Field of Search ..... 623/6, 1, 11, 66; 427/2.24, 2.25, 412.1, 412.2, 412.3, 412.4, 412.5; 351/160 R

[56] References Cited

U.S. PATENT DOCUMENTS

2,999,056	9/1961	Tanner	522/118
3,228,741	1/1966	Becker	351/160 R
3,880,818	4/1975	Shen et al.	526/322
3,925,178	12/1975	Gesser et al.	204/165
3,944,709	3/1976	Levy	428/409
3,959,105	5/1976	Feneberg et al.	204/165
3,961,379	6/1976	Highgate	522/116
3,985,697	10/1976	Urbach	523/106
4,055,378	10/1977	Feneberg et al.	351/160
4,072,769	2/1978	Lidel	427/38
4,096,315	6/1978	Kubacki	428/412
4,099,859	7/1978	Merrill	351/160 H
4,122,942	10/1978	Wolfson	206/5.1
4,123,308	10/1978	Nowlin et al.	427/41
4,131,691	12/1978	Morley et al.	427/41
4,137,365	1/1979	Wydeven et al.	428/412
4,143,949	3/1979	Chen	427/41
4,189,364	2/1980	Aelion et al.	522/4
4,214,014	7/1980	Hofer et al.	427/40
4,240,163	12/1980	Galin	623/6
4,277,595	7/1981	Deichert et al.	528/26
4,311,828	1/1982	Imada et al.	528/483
4,312,575	1/1982	Peyman et al.	351/160 H
4,328,257	5/1982	Muehlberger et al.	427/34
4,344,981	8/1982	Imada et al.	427/40
4,405,773	9/1983	Loshaek et al.	526/318.42
4,409,258	10/1983	Feurer et al.	427/38
4,430,458	2/1984	Tighe et al.	523/108
4,463,148	7/1984	Hofer et al.	526/264
4,478,873	10/1984	Masso et al.	427/40
4,560,458	12/1985	Ueno et al.	204/165
4,632,842	12/1986	Karwoski et al.	427/2
4,656,083	4/1987	Hoffman et al.	427/41
4,718,907	1/1988	Karwoski et al.	623/12
4,720,512	1/1988	Hu et al.	523/112
4,731,079	3/1988	Stoy	623/6
4,731,080	3/1988	Galin	623/6
4,806,382	2/1989	Goldberg et al.	623/6 X
4,836,884	6/1989	McAuslan	427/2.24 X
4,851,003	7/1989	Lindstrom	427/2.24 X
4,851,009	7/1989	Pinchuc	427/2.25 X
4,865,870	9/1989	Hu et al.	427/2
4,885,077	12/1989	Karakelle et al.	427/41
4,919,659	4/1990	Horbett et al.	427/2
4,927,676	5/1990	Williams et al.	427/2
4,959,074	9/1990	Halpern et al.	623/6 X
4,979,959	12/1990	Guire	623/6 X
5,002,582	3/1991	Guire et al.	623/66
5,091,204	2/1992	Ratner et al.	427/2
5,171,267	12/1992	Ratner et al.	623/6
5,252,628	10/1993	Chirila et al.	623/6 X

FOREIGN PATENT DOCUMENTS

2119957	11/1983	United Kingdom	351/160 R

OTHER PUBLICATIONS

H. Yasuda, "Plasma for Modification of Polymers", *J. Macromol. Sci.–Chem.*, A10(3), pp. 383–420 (1976).

Knight et al., "Surface Modification of Intraocular Lenses to Reduce Corneal Endothelial Damage", *AM Intra–Ocular Implant Soc.* J–vol. V, pp. 123–130, Apr. 1979.

Gazard et al., "Lithographic Technique Using Radiation–Induced Grafting of Acrylic Acid into Poly (–Methyl Methacrylate) Films", *Polymer Engineering and Science*, vol. 20, No. 16, pp. 1069–1072 (1980).

K. L. Mittal, "Interfacial Chemistry and Adhesion: Recent Developments and Prospects", *Pure & Appl. Chem.*, vol. 52, pp. 1295–1305 (1980).

Akovali et al., "Polymerization of Hexamethyldisiloxane by Plasma on Activated Charcal: Investigation of Parameters", *Journal of Applied Polymer Science*, vol. 29, pp. 2617–2625 (1984).

Lui et al., "Polymethyl Methacrylate Resist Sensitivity Enhancement in X–Ray Lithography by In Situ Polymerization", *Appl. Phys. Lett.*, 44(10), pp. 973–975, May 15, 1984.

Keates et al., "Coated Intraocular Lenses", *Ophthalmic Surgery*, vol. 18, No. 9, pp. 693–697 (1987).

Primary Examiner—David J. Isabella

Attorney, Agent, or Firm—Panitch Schwarze Jacobs & Nadel, P.C.

[57] ABSTRACT

A method of permanently modifying the surface of a substrate material so as to develop a microscopically smooth, biocompatible surface thereon comprises covalently grafting a biocompatible polymeric material to the surface of the substrate material by radio frequency plasma-induced grafting. The biocompatible polymeric material is preferably the same as the substrate material. In addition, a method of permanently modifying the surface of a substrate material comprises subjecting the substrate surface to radio frequency plasma sufficient to raise the temperature at the substrate material to just above the glass transition temperature (T_g) of the substrate material for a time sufficient to produce a microscopically smooth, biocompatible surface on the substrate material. Further, a prosthesis used in mammals, including an intraocular lens, comprises a polymeric material core and a biocompatible polymeric material covalently grafted to the polymer core by radio frequency plasma induction.

6 Claims, No Drawings

BIOCOMPATIBLE, SURFACE MODIFIED MATERIALS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a division of U.S. patent application Ser. No. 07/820,169, filed Jan. 13, 1992, now U.S. Pat. No. 5,260,093, which was a continuation-in-part of U.S. patent application Ser. No. 07/342,270, filed Apr. 24, 1989, now issued as U.S. Pat. No. 5,080,924.

FIELD OF THE INVENTION

The present invention relates to methods of permanently modifying the surface of materials by plasma-induced and, where desired, post-plasma reactions to produce biocompatible, surface modified materials. In addition, the present invention relates to biocompatible, surface modified prostheses and, in particular, to a biocompatible, surface modified intraocular lens used in mammals.

BACKGROUND OF THE INVENTION

Prosthetic devices or prostheses are commonly used in medical procedures replacing or augmenting defective organs in mammals and humans, in particular, and are numerous and diverse in structure and application. Examples of prostheses include artificial joints, valve replacements, skin grafts, vascular grafts, shunts, plates and contact and intraocular lenses. Typically, prosthetic devices comprise natural and/or synthetic materials which are abrasive on the cellular level. Various prostheses in current use or in experimental use comprise metals, ceramics, silicone rubbers, polyesters, polyurethanes and/or polysulfones. Synthetic polymers, such as polymethylmethacrylate (PMMA) and hydroxyethylmethacrylate (HEMA), for example, are preferred polymers for prosthetic use in general and contact lenses and intraocular lenses in particular.

PMMA, for example, has several beneficial characteristics for such prosthetic use, including excellent light transmission, good optical clarity, resistance to fluid diffusion and in vivo deterioration, ease in processing (injection molding or machining, for example) and ease in implantation, such as an intraocular lens, an artificial joint and other implantable prostheses.

Typical lens prostheses, for example, are manufactured by machining, which leaves circular lathe marks or grooves visible at even relatively low magnification. These machining remnants render the lens unusable until the surface is smoothed, typically by a mechanical polishing process. However, the conventional polishing process generally takes several days to complete, has a failure rate in excess of 30% and fails to produce a microscopically smooth surface.

Abrasive prostheses, especially those which are implanted, can cause tissue irritation, edema and scarring. For example, posterior lens capsule opacification is a prevalent problem among those patients who have received intraocular lens implants comprising conventionally polished PMMA and other similar materials.

It is desirable to modify the surface properties of such abrasive materials without changing the beneficial characteristics thereof by developing a smooth surface thereby discouraging tissue adhesion and inhibiting cellular growth. Prostheses which do not promote tissue adhesion and do not inhibit cellular growth and which are not otherwise toxic to living systems may be considered "biocompatible." Surface modification to develop a biocompatible surface should be resistant to deterioration over time and should have no adverse effects on tissues and cells with which the surface modified material comes in contact.

Those skilled in the art have long recognized the need for biocompatible, surface modified materials for use in prosthetic devices and other materials. For example, U.S. Pat. No. 3,961,379 discloses a bioimplantable device manufactured from a cross-linked, swollen, hydrophilic polymer. These modified polymers must be solid and must be swellable by fluid swelling substances. Once swollen, the solid polymer is polymerized with a modifying substance by, for example, high energy particle radiation.

U.S. Pat. No. 4,189,364 discloses hydrophilic polymers formed in situ by irradiating a mixture of hydroxyalkyl methacrylate and a cross-linking agent. This patent discloses a process for forming hydrophilic polymer articles or hydrophilic polymer coatings on other substrates, such as glass or plastic, by polymerizing a hydrophilic monomer system by high energy particulate irradiation, such as accelerated electrons or nuclear particles including neutrons, protons, alpha, beta and/or gamma particles.

Radiation-induced grafting of acrylic acid onto other polymer films is disclosed by Gazard, M. et al., "Lithographic Technique Using Radiation-Induced Grafting of Acrylic Acid Into Poly(Methyl Methacrylate) Films," *Polymer Engineering and Science*, 20:16 (1980). Gazard et al. disclose that, under ionizing radiation, polymers undergo changes in their properties, especially in their solubility. Ionizing radiation of polymers leads to the formation of free radicals and other intermediates, which may be used to initiate the grafting of a monomer to produce a grafted copolymer with properties different from those of the initial polymer. For example, irradiated PMMA, onto which acrylic acid is grafted produces a graft copolymer which is insoluble in the solvents of PMMA.

U.S. Pat. No. 2,999,056 also discloses that an unsaturated organic acid may be attached to a shaped polymeric structure by ionizing radiation.

Other methods of altering the surface of polymeric objects include exposing the surface of a polymeric article to low temperature plasma or an electrically charged gaseous atmosphere, followed by contacting the surface of the polymeric article with a surface modifying compound as described, for example, in U.S. Pat. No. 4,344,981. This two-step method is generally called plasma-induced coating. Plasma induction has been described generally in U.S. Pat. No. 4,328,257, Yasuda, "Plasma for Modification of Polymers," *J. Macromol. Sci. C. Chem.*, 10(3):383 (1978), Mittal, "Interfacial Chemistry and Adhesion: Recent Developments and Prospects," *Pure & Appl. Chem*, 52:1295 (1980), Akovali, G. and Hastrel, N., "Polymerization of Hexamethyldisiloxane by Plasma on Activated Charcoal: Investigation of Parameters," *J. Appl. Polymer Sci.*, 29:2617 (1984) and Liu, W. T. et al., "Polymethyl Methacrylate Resist Sensitivity Enhancement in X-Ray Lithography by In Situ Polymerization," *Appl. Phys. Lett.*, 44:973 (1984), for example.

Ionized vapor or plasma discharge is typically created in a vacuum chamber in which the object to be modified is placed. The plasma discharge conditions the surface by creating free radicals and/or ions. It is known, for example, that exposing the surface of an object to plasma discharge, such as an oxygen plasma, enhances the wettability or hydrophilicity of such a surface. However, such treatment is only temporary. U.S. Pat. Nos. 3,925,178; 3,944,709; 4,072,769; 4,096,315; 4,122,942; 4,123,308; 4,131,691; 4,137,

365; 4,214,014 and 4,478,873 disclose examples of polymers whose surface characteristics have been modified by a plasma discharge.

Plasma discharge treatment may also be used to prepare an object for the attachment or grafting of a compound or material to the plasma discharge treated object. For example, a plasma discharge step may be used to condition the surface for grafting by creating free radicals to which a compound or material may be grafted. Such compounds or materials are generally called surface modifiers. Knight, P. M. et al., in "Surface Modification of Intraocular Lenses to Reduce Corneal Endothelial Damage," *Am. Intra-ocular Implants Soc. J.*, 5:123 (1979) disclose one example of a polymer object having a surface modifier attached thereto using gamma irradiation and radio frequency (RF) gas plasma treatment to generate free radicals on the surface of a PMMA intraocular lens followed by polymerizing hydrophilic monomers, in particular, HEMA and vinyl pyrrolidone, as a coating on the surface of the lens. While the coated surfaces exhibited enhanced hydrophilicity, the coated surfaces were not stable when boiled to sterilize them. Surface modification by gamma radiation followed by polymerization on the surface, on the other hand, remained intact through several hours of boiling. However, such coated PMMA surfaces were damaging to rabbit endothelial cells and surfaces coated with dissolvable coatings, such as polyvinyl acetate, were preferred.

Another example of a surface treated polymer is disclosed in U.S. Pat. No. 4,312,575. This patent discloses a soft, highly oxygen permeable, hydrophobic polymeric lens which has on its surface an ultra-thin, optically clear, permeable barrier coating which is the reaction product resulting from a glow discharge polymerization process conducted in a hydrocarbon or halogenated hydrocarbon gaseous atmosphere. While the plasma discharge process, itself, results in a hydrophilic surface, subsequent exposure to a glow discharge atmosphere of oxygen or ambient oxygen yields a still more hydrophilic surface.

U.S. Pat. No. 4,409,258 discloses a method for rendering contact lenses hydrophilic by bombarding the lens, which may be PMMA or silicone, with a positive ion beam generated by a plasma discharge, such as an oxygen plasma. The lens is thereafter hydrated, preferably at an elevated temperature.

Examples of surface treated polymeric lenses for use in humans are included in U.S. Pat. No. 3,880,818. This patent discloses a soft contact lens that is flexible and physiologically compatible, which is made by manufacturing a hard, inflexible prepolymer, such as a hard acrylic acid-type polymer, and reacting the inflexible prepolymer with an alcohol to esterify pendant carboxyl groups with alkyl groups, hydroxy alkyl groups or alkoxyalkyl groups, containing no more than eleven carbon atoms.

U.S. Pat. No. 4,143,949 discloses a discharge polymerization and coating process for making a hydrophilic contact lens from an oxygen permeable, hydrophobic polymer. The hydrophobic lens is placed in a glow discharge apparatus containing an atmosphere comprising a polymerizable organic monomer, such as hydroxyalkyl acrylate or methacrylate, glycidyl methacrylate, propylene oxide or N-vinyl-2-pyrrolidone, where the glow discharge is used to polymerize the monomer onto the surface of the contact lens.

Other examples of surface treated polymeric objects include U.S. Pat. Nos. 3,228,741; 3,925,178; 3,959,105; 3,985,697; 4,055,378; 4,277,595; 4,405,773; 4,430,458; 4,463,148; and 4,731,080. U.S. Pat. No. 4,731,080, for example, discloses a coated intraocular lens having a hydrophobic cross-linked vinyl-containing silicone polymer placed on the lens surface in solution.

It would be desirable to have a biocompatible, surface modified material and a method for producing the same, where the surface modification is substantially permanent, results in a smooth surface on the cellular level and where the surface modified material may be used, inter alia, as a prosthetic device in mammals. One such method is disclosed in U.S. Pat. No. 5,080,914, filed Apr. 24, 1989, the disclosure of which is incorporated herein by reference.

BRIEF SUMMARY OF THE INVENTION

According to the present invention, a method of permanently modifying the surface of a polymeric substrate material so that the substrate material develops a microscopically smooth, biocompatible surface comprises covalently grafting a biocompatible polymeric material to the surface of the substrate material by radio frequency plasma-induced grafting where the biocompatible polymeric material comprises substantially the same material as the material forming the substrate.

In addition, the present invention is directed to a method of permanently modifying the surface of a substrate material so that the substrate material develops a microscopically smooth, biocompatible surface comprising subjecting the substrate surface to radio frequency plasma sufficient to etch the substrate surface and raise the temperature at the surface to a temperature just above the glass transition temperature (T_g) of the substrate material.

Further, the present invention is directed to a prosthesis used in mammals comprising a polymer substrate or core and a biocompatible polymeric material grafted to the polymer core by plasma induction, the biocompatible polymer material comprising substantially the same material as the material forming the substrate.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Although the methods of preparation of the invention apply generally to the preparation of permanent surface modification of many different materials, the methods are described and exemplified below with specific examples using polymeric intraocular lenses as prostheses which may be used in mammals. It will be understood by one skilled in the art that the methods of the present invention may be used to prepare permanently modified surfaces of other substrate materials, such as those prosthestic materials identified above. Moreover, it will be apparent to one skilled in the art that the methods of the present invention readily lend themselves to the preparation of materials having modified or enhanced surface characteristics having other uses.

According to one embodiment of the present invention, a biocompatible polymeric material is covalently grafted to the surface of a substrate material by radio frequency plasma induction. Examples of substrate materials to which a biocompatible material may be grafted include polymers, such as silicone, polypropylene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, PMMA, polyacrylic acid, or polymers of HEMA, ethylenediamine, diethylenetriamine, allylamine, hexamethyl-disiloxane, silazane and N-vinyl pyrrolidone.

Generally, the substrate material used in accordance with the present invention is chosen dependent upon its intended use. For example, PMMA and HEMA are two materials of

choice for use in prosthetic devices intended for implantation or other application in mammals. However, in view of the present specification, one skilled in the art will appreciate that any organic polymer may be used as a substrate material, as well as certain ceramics and metals. Where an optically clear polymer for use in prosthetic devices for mammals is the substrate material, it is presently preferred that the polymer comprises PMMA.

The surface of the substrate material is modified by grafting a biocompatible polymeric material to the surface thereof. In some cases where it is desired to have only one material present, the first biocompatible polymeric material is substantially the same as the material forming the substrate. Once the substrate material surface has been modified by covalently grafting the biocompatible material to the surface of the substrate material, the modified surface should have properties which are relatively nontoxic and nonirritating to living tissues. In addition, the modified surface should not adversely affect the desired properties of the remainder of the substrate material, such as structural integrity and optical clarity, among others. In addition, the modified surface should be microscopically smooth. As used herein, the term "microscopically smooth" shall mean that the surface of the modified substrate should be featureless upon examination at an enlargement of about 3,000 to about 10,000×. In addition, where desired and depending on the properties of the first biocompatible polymeric material, the modified surface should be absent crystallinity, cross-linked and thermally stable.

Where the substrate material is intended for use in or as a prosthetic device, such as an intraocular lens, the surface modification of the present invention should not adversely affect the transparency or ocular acuity of the substrate material. Further, the first biocompatible material to be grafted to the substrate surface preferably comprises a material that is relatively easy to polymerize in a gas plasma environment. Such materials include unsaturated compounds or those compounds containing nitrogen, silicone or halogen. Materials that are relatively difficult to polymerize in a gas plasma environment include saturated compounds, cyclic compounds, compounds with a high molecular weight, such as proteins, and those compounds containing oxygen.

Examples of presently preferred biocompatible polymeric material include polyacrylic acid, silicone, polypropylene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, polymethylmethacrylate or polymers of ethylenediamine, diethylenetriamine, allylamine or hydroxyethylmethacrylate.

The biocompatible polymeric material should be grafted to the substrate material in a relatively uniform thickness and texture along the surface of the substrate material. In addition, especially where it is desired to use the substrate material as a prosthetic lens, it is preferred that the biocompatible polymeric material is present on the surface of the substrate material in a relatively small thickness to prevent interference with the optical clarity of the lens. More preferably, the biocompatible polymeric material is present in a monomolecular layer. In one embodiment of the present invention, for example, a surface modified substrate comprises a biocompatible polymeric material grafted to the surface of a substrate material with a biocompatible polymeric material thickness of about 100 A.

Grafting of the biocompatible polymeric material according to the present invention is conducted using radio frequency plasma-induced grafting. Other methods of grafting, such as electronic or ultra-violet (UV) radiation are not suitable where it is desired (as it is here) to modify only the surface of the substrate material. For example, where a prosthetic lens, such as a contact lens or intraocular lens, is desired to be modified, modification should be confined to the surface of the lens to avoid affecting the optical properties of the lens. Radio frequency plasma-induced grafting according to the present invention avoids structural modification below the outer-most surface layer, and generally results in more desirable optical properties.

Such gas plasma-induced grafting may be conducted in a radio frequency gas plasma reactor capable of generating a frequency of about 1 MHz to about 40 MHz. The frequency generated by a typical commercial gas plasma reactor is about 13.56 MHz, although one skilled in the art will recognize that higher and lower frequencies may be used to graft the biocompatible polymeric material to the surface of the substrate material in a radio frequency gas plasma reactor, depending on the substrate material and biocompatible polymeric material used, the relative ease or difficulty in preparing the surface of the substrate material for grafting, the relative ease or difficulty of vaporizing or polymerizing the biocompatible material, among other factors.

The first step of radio frequency plasma treatment according to this invention is the removal or etching of material from the surface of the substrate material being bombarded by the plasma. This process cleans the substrate and produces active species on the surface so treated, such as ions and free radicals, which can be used for inducing a graft reaction.

Generally, the rate of material removal may be controlled relative to the rate of deposition of a graft polymer by the frequency of the gas plasma, the power of the gas plasma, the treatment time, the gas used in the plasma, the gas pressure/concentration, and the type of bond desired on the treated substrate material surface, depending on the particular substrate material.

Plasma-induced grafting of the biocompatible polymeric material to the substrate material may be conducted in radio frequency plasma reactors known in the art. The Branson model 3003-1813 is one example of a suitable radio frequency gas plasma reactor which may be used to create a suitable gas plasma atmosphere in which a first biocompatible material having the properties described above may be vaporized and polymerized for grafting. One skilled in the art will appreciate, however, that other plasma reactors and apparatus may be used in accordance with the present invention.

Preferably, the ambient gas used in the radio frequency gas plasma-induced grafting is selected from the group consisting of nitrogen, ammonia and argon and other noble gases. More preferably, the gas used in the radio frequency gas plasma reaction is argon. Argon is an inert gas which creates active sites but does not produce new bonding when applied to a substrate surface in a RF gas plasma reactor. Oxygen, on the other hand, for example, tends to produce peroxides in such plasma-induced grafting reactions and is, therefore, generally less desired. Where no biocompatible material is to be grafted to the substrate surface (discussed below) or where the presence of reactive gas molecules on the substrate surface is not desired, it is presently preferred to use noble gas as ambient gas in the radio frequency gas plasma reactor, such as argon. One skilled in the art will be readily able to determine in view of this disclosure which suitable gases may be used in the plasma reaction in accordance with the present invention.

Surface modification by plasma-induced grafting in accordance with one embodiment of the present invention essentially comprises two steps: (1) plasma treatment or preparation of the substrate surface; and (2) introduction of the monomer of the biocompatible polymeric material into the plasma where the monomer becomes grafted to the substrate surface. As discussed above, the plasma treatment of the substrate surface breaks surface bonds, generating ions and free radicals at the surface of the substrate material, thus "activating" the surface. Introduction of the monomer into the radio frequency induced plasma causes the monomer to react with the substrate surface, polymerize and become grafted to the substrate surface.

The length of time the biocompatible material in an induced plasma state should be allowed to react with the substrate material depends upon several factors, including the plasma or radiation power, the radio frequency, the flow concentration or pressure, the temperature and the desired thickness of the grafted material. Preferably, the radiation power is about 10 watts to about 200 watts, depending upon the biocompatible material. For example, where the biocompatible material comprises silazane, hexamethyldisiloxane, PMMA, NVP or PAA, it is presently preferred that the radiation power is about 50 watts. Where the biocompatible layer material comprises HEMA (discussed below), it is presently preferred that the radiation power is about 10 watts to about 100 watts. In any event, except where desired, the reactor power used and the duration such power is used should be low and/or short enough so as to not induce thermal circulation and melt the substrate material. For example, where the substrate material comprises PMMA, the reaction conditions (i.e., power and duration) should not increase the temperature of the substrate material above about 40°–45° C. One skilled in the art may readily determine, in view of the plasma reaction variables described above, the desired plasma radiation power to be used in accordance with the present invention.

The plasma reaction is preferably conducted for a period of time of about 1 minute to about 60 minutes. More preferably, the plasma reaction is allowed to occur for a period of time of about 15 minutes to about 30 minutes. The flow concentration or vapor pressure of the plasma reactants in the reactor chamber should be low enough so that the particular monomer of the biocompatible material vaporizes when introduced into the reactor. Preferably, the vapor pressure is about 0.1 torr to about 0.6 torr. More preferably, the vapor pressure is about 0.4 torr.

The temperature in the plasma reaction should not be allowed to approach those temperatures which may damage the substrate material or the biocompatible material. High radiation power and any polymerization reaction (i.e., polymerization which may occur when the grafting reaction occurs; e.g.: polymerization to polymethylmethacrylate) tend to increase the temperature of the plasma reaction. It is desirable, therefore, to maintain the temperature in the plasma reaction below the temperature at which the substrate material and/or the graft material will be damaged, typically below about 40°–50° C.

In another embodiment of the present invention where no biocompatible material is grafted to the substrate, a microscopically smooth surface is obtained by plasma treatment of the substrate surface sufficient to etch the substrate surface and raise the temperature at the substrate surface to a temperature just above the glass transition temperature (T_g) of the substrate material. While not wishing to be bound by any particular theory, the inventors believe that, plasma treatment to induce an increase in temperature causes a thermal annealing at the surface of the substrate whereby irregular surface features (such as surface peaks, etc.) relax, evening out such irregularities. Where temperatures above the glass transition temperature are desired, relatively higher radiation power is preferred. For example, to reach a surface temperature of about 105° C., which is the glass transition temperature of PMMA, radiation power of about 100 to about 120 watts is preferred. One skilled in the art may readily determine glass transition temperature by reference to publicly available materials characteristics tables and determine the temperature obtainable at a given wattage in a given reactor factoring in time, efficiency of the reaction chamber and the surface area of the substrate, for example. The radiation power used and the time the substrate is exposed to such radiation should be such to avoid thermal circulation of the substrate beneath the surface and melting of the substrate.

In view of this disclosure, one skilled in the art may readily determine the reactants, time, pressure and temperature conditions for a reaction using given materials without undue experimentation. For example, in one embodiment of the present invention, methyl methacrylate liquid is introduced into a plasma reactor chamber having a plasma-etched or treated body of PMMA where, because of the low pressure within the chamber, the methyl methacrylate vaporizes. The methyl methacrylate is exposed to about 50 to about 150 watts of radio frequency radiation at about 27.5° C. at a reactant or vapor pressure of about 0.4 to about 0.5 Torr.

Novel products having a permanently modified surface resulting from the method of the present invention include prostheses, such as an intraocular lens, for use in mammals having a permanently modified, biocompatible surface, which comprises a polymer lens body and a biocompatible, polymeric material grafted thereto, where the biocompatible, polymeric material comprises substantially the same material as the material forming the polymer lens body, such as PMMA.

In addition, novel products produced using the method of the present invention include prostheses for use in mammals comprising a polymeric material substrate having a permanently modified surface where the surface was modified by subjecting the substrate surface to radio frequency plasma sufficient to raise the temperature at the substrate surface to just above the glass transition temperature.

The invention will now be illustrated in further detail by reference to the following specific, non-limiting examples.

EXAMPLE I

An intraocular lens manufactured by CILCO from PMMA was abraded using 1 micron aluminum oxide particles to produce grooves on the surface of the lens of 1 micron depth. Macroscopically, the lens had a hazy appearance. The lens was cleaned in a 1% sodium dodecyl sulfate (SDS) solution and then thoroughly rinsed in deionized water to remove any contaminants that may be present from the manufacturing process or subsequent handling. The lens was positioned in a Branson 3000 Series radio frequency plasma reactor in a glass treatment fixture. The pressure inside the reactor was reduced to less than about 0.1 Torr for approximately 10 minutes. Argon gas (Ar) was then introduced at approximately 8 psi and the pressure inside the reactor was adjusted to 0.5 Torr for 10 minutes to purge the chamber with the argon gas. Radio frequency power was then turned on to 120 watts while maintaining chamber pressure at 0.5 Torr. Treat-

ment with the argon gas plasma continued for approximately 60 minutes. After this time, radio frequency power was turned off and the chamber was purged to normal atmospheric pressure to open the chamber door. Macroscopically, the lens appeared clean and clear. Upon microscopic examination, some surface irregularities or memory of the initial grooves was apparent.

EXAMPLE II

An intraocular lens was treated using the procedures of Example I. After turning off the radio frequency power, the chamber was then pumped down to a pressure of 0.1 Torr for approximately 5 minutes to evacuate the chamber. Methylmethacrylate (MMA) monomer was then introduced into the reactor chamber at maximum flow rate (approximately 0.8 Torr) and radio frequency power was turned on to 70 watts for 30 minutes. After this time, MMA delivery was discontinued and the radio frequency power was shut down. The chamber was then purged to normal atmospheric pressure to open the chamber door. Macroscopically and microscopically, the lens was free of any surface irregularities, surpassing the surface quality of the original, commerical lens.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than the specification, as indicating the scope of the invention.

We claim:

1. A prosthesis for use in mammals comprising a polymeric substrate material having a permanently modified microscopically smooth, biocompatible surface thereon, produced by covalently grafting a polymeric biocompatible material to the surface of the substrate material by radio frequency plasma induction, the biocompatible polymeric material comprising substantially the same material as the polymeric substrate and being physically grafted by covalent bonds to the substrate material, and the modified microscopically smooth, biocompatible surface being substantially free of surface irregularities at a magnification of at least 3,000x.

2. The prosthesis according to claim 1, wherein the biocompatible polymeric material is selected from the group consisting of polyacrylic acid, silicone, polypropylene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, polymethylmethacrylate and polymers of ethylenediamine, diethylenetriamine, allylamine or hydroxyethylmethacrylate.

3. A prosthesis used in mammals having a permanently modified, microscopically smooth, biocompatible surface comprising:

(a) a polymeric material core; and

(b) a biocompatible polymeric material covalently grafted to the surface of the polymeric material core by radio frequency plasma induction, the biocompatible polymeric material comprising substantially the same material as the core.

4. The prosthesis according to claim 3, wherein the polymeric material is selected from the group consisting of polyacrylic acid, silicone, polypropylene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, polymethylmethacrylate, and polymers of ethylenediamine, diethylenetriamine, allylamine or hydroxyethylmethacrylate.

5. An intraocular lens having a permanently modified, smooth, biocompatible surface, comprising a polymeric material lens body, and a biocompatible polymeric material, said biocompatible polymeric material being covalently grafted to the surface of the lens body by radio frequency plasma induction and comprising substantially the same material as the body.

6. The intraocular lens according to claim 5, wherein the biocompatible polymeric material is selected from the group consisting of polyacrylic acid, silicone, polypropylene, polyester, polytetrafluoroethylene, polyethylene terephthalate, polyurethane, polymethylmethacrylate and polymers of ethylenediamine, diethylenetriamine, allylamine or hydroxyethylmethacrylate.

* * * * *